Diabetes in Old Age

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Preface

Diabetes in Old Age, 4th Edition

The primary purpose of this book is to promote high-quality diabetes care for all older people irrespective of their health or social care setting. This brings with it the equally important need to ensure their wellbeing, quality of life, and an acceptable level of physical and cognitive functioning.

Older people also have a fundamental right to expect this care to be delivered in a compassionate and effective way using, where possible, all modern treatments and technology. With this view in mind, we decided at an early stage of the preparation of this book that individual contributions should be provided by active investigators in the field, many of whom are leading international authorities, rather than by armchair physicians and clinicians. Our expert contributors come from the USA, Europe, Australia, Canada, India, Mexico, and South America.

We have also tried to establish a balance between diabetes care in community settings and care in hospital or care homes. All these aspects and more are covered. We have included a "Key messages" section in each chapter and have limited the number of references cited where possible in an attempt to cite more recent work.

This book has been written to appeal to general physicians, diabetologists, geriatricians, hospital-based and community nurses, diabetes specialist nurses, social care staff, commissioners of health and social services, policy makers, and other allied professional staff and stakeholders.

This edition gains from the inclusion as new editors three highly distinguished clinical scientists, Trisha Dunning, Medha Munshi, and Leocadio Rodriguez Manas, who have worked tirelessly with Alan J. Sinclair to produce this book.

Finally, we wish to acknowledge the administrative support of Caroline Sinclair.

Alan J. Sinclair, Medha Munshi, Leocadio Rodriguez Manas, and Trisha Dunning

Foreword

The cognoscenti, the small cadre of experts on diabetes in older people, will skip this foreword and dive right into the individual chapters. There they will find many treasures related to clinical science and clinical care, as well as historical vignettes and current controversies related to diabetes in aging patients.

You, by reading this foreword in a book on diabetes in old age, are marking yourselves as non-expert but you are clearly ahead of your medical colleagues. You are recognizing that the excellent textbooks on diabetes and excellent textbooks on geriatric medicine, though they cover medical care of the older patient, typically fall short in dealing with the older patient with diabetes.

These textbooks mirror the state of affairs in medical care today. When I was a young physician, I was impressed that excellent internists provided excellent care for their patients, including very good diabetes management. My impression now is that very good internists continue to provide very good care, except for diabetes where the care often is only mediocre. Many endocrinologists, formerly excellent in diabetes, are also falling further and further back from the cutting edge of diabetes care. This is especially sad because we now know more than ever the importance of good management and have better tools with which to approach the desired goals. The gap between "excellent" and "actual" widens as the patient's age increases.

In this essay, I plan to inspire you, to help guide you into a highly satisfying professional path, a path that will please you, as well as enhance your value to your patients and to your medical community. The rest of this book is filled with instructional material that you will find very useful. My goal is to provide an overarching view from the top of the mountain.

Nourishing the soul

Champions seek new challenges, set new goals. For mountain climbers and cellists, surgeons and swimmers, dancers and authors, striving for excellence channels energies and rejuvenates the self. The physician who adopts the mindset of a champion helps his or her patients, helps other health care professionals with their patients and nourishes his or her own soul. At this time in medicine, when physician burnout is epidemic, nourishment for the soul can be life-saving. In the USA, where the pension systems are in disarray and large debts have been piled up to pay for schooling, physicians will be working many years past the hallowed 65. The best preparation for the long journey is passion in one's professional pursuit. As an internist, or endocrinologist, or geriatrician, join me in exploring the attractions of becoming skilled in the care of diabetes of the old.

When I entered the profession fifty years ago, antibiotics were routing many infectious diseases. The ancient aphorism "If you know syphilis, you know all of medicine" was being re-modelled; syphilis was replaced by diabetes.

I propose a new model: "If you know diabetes in old age, you know all of medicine".

The challenge for the profession

Increasingly, medicine in general is benefiting from the introduction of protocols and algorithms. While improving care, these also shrink the intellectual distance between the physician, the physician's assistant and the nurse. I am guessing that a 37-year-old professor of computer science with type 1 diabetes can probably manage well with a little help from a diabetes educator and an occasional visit to a physician. Recall the World War II pharmacist's mate who in the pre-antibiotic area successfully removed an inflamed appendix from a crew member of his submarine submerged beneath the waters of the Pacific.

Advancing age brings growing complexity. Elderly patients with diabetes need continuous input from skilled physicians. For these physicians, protocols and algorithms are the starting point but the real plan needs

multiple modifications, surveillance, balancing of competing priorities, and skilled navigation of poorly charted waters. It demands professional skills at their best.

Interpreting data

Multi-centre trials, the foundation of therapeutics today, are typically performed on younger patients. With the basic and clinical science in the background, the data from widely heralded multi-centre trials (with patients who are typically younger and less complicated) provide a basis but not a recipe for care of the elderly patient. Advanced age and other exclusionary criteria, including medications, make extrapolations to older people more tenuous. The loud "microphones" supported by pharmaceutical company coffers often fill the air with information that is misleading for older patients.

Laboratory standards are based on younger populations. Data in the elderly are much sparser. Even when the mean and median for a lab test remain unchanged, the splay typically increases so that higher and lower values that are "normal" for an older patient are easily labelled as pathological.

New medications are largely tested on younger, less complicated patients. Data among older patients are sparse. Many side effects of drugs emerge gradually in the years after their introduction. The catalogue of side effects among older complex patients emerge more slowly. The sparseness of data dictates that new drugs should be avoided in older patients, except on the very rare occasion when the new drug is a very substantial advance and other drugs cannot meet the need.

Adverse drug interactions between two drugs are identified slowly. Many remain undetected. Typical elderly patients take many medications, exponentially increasing the likelihood of adverse drug interactions and, equally, making their detection most difficult.

Depression

Advancing age as well as medications and multiple medical conditions are associated with depression. The link between diabetes and depression has received a lot of attention recently. Growing evidence that depression impacts negatively on physical health mandates that depression, so common in older people, be detected and treated energetically.

In dealing with depression, especially in the older patient, recall:

I Depression without sadness is easy to miss.

II Screening instruments are helpful.

III Personalized rationalizations of the healthcare professional ("If I were 82 and living alone, I would also feel that way …") can obscure the correct diagnosis and management.

IV Drugs as well as endocrine diseases and other disorders are common aetiologies of depression that is reversible.

V When medication and psychotherapy fail, ECT (electroconvulsive therapy), is an excellent therapeutic choice to consider.

VI With ageing, suicide rates rise sharply, especially among white males. Living alone and having firearms in the home each add to the risk.

Demographics and disease

The population is being enriched progressively with patients who are over 65. They are living longer. The so-called old-old are a rapidly growing group. Objective data to guide the physician require ever longer lines of extrapolation, demanding more of the physician's judgment. The incidence and prevalence of diabetes increase with age. Ageing brings out diabetes; diabetes accelerates biological ageing and onset of other pathology. These processes corrode cognition.

Ageing in our Society: The universal reverence, or at least respect, for the elderly that held sway worldwide since the beginning of human memory, has been replaced in the industrialized world of today with a wide range of negative attitudes, mostly undeserved. In their care for the elderly, physicians and their teammates in care will be energized by recalling the widely appreciated positive features of a majority of the elderly:

I Every older patient can be improved in some way by an encounter with a professional.

II Typically, older people are appreciative of the care and express their appreciation.

III Their expectations for improvement are realistically tempered.

IV They are individually "more unique".

"More unique" is a phrase that will galvanize to action legions of amateur grammarians all over the English-speaking world. They will reflexly remind me that unique indicates one-of-a-kind and therefore no

comparator is permitted. Biology and I will prove them wrong. Let's start with a fertilized egg that is just dividing to generate a pair of monozygotic twins. They are not identical and progressively diverge, distancing one biological self from the other. All humans do the same. The extremely similar looking zygotes, and highly similar looking newborns progressively diverge, biologically, sociologically and medically, to the delight and amazement of the skilled physician and other health care providers. Like snowflakes, Rembrandt paintings, precious gemstones, and leaves from a single tree, blessedly, there are no sames among older patients with diabetes.

Valediction

With a little luck, it is likely that you, in your lifetime, will never lack for food for your body. Much more at risk, and therefore more to be guarded, is the supply of nourishment for your professional soul.

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SECTION A

Pathophysiology, screening and diagnosis

CHAPTER 1
Pathophysiology of diabetes in older people

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KEY MESSAGES

- Lifestyle factors play a major role in diabetes in the elderly.
- Diabetes in the elderly is metabolically distinct.
- Elderly patients with diabetes have an increase incidence of severe or fatal hypoglycemia.

1.1 Introduction

Numerous studies have been conducted to investigate the pathogenesis of type 2 diabetes [1]. Unfortunately, elderly patients were systematically excluded from these protocols. We have more recently started to study, in a systematic fashion, the pathophysiological alterations that occur in elderly patients with diabetes. These studies, the details of which will be reviewed in the following sections, suggest that there are many ways in which diabetes in the elderly is unique. Some of the factors that contribute to the high prevalence of diabetes in the elderly are shown schematically in Figure 1.1.

1.1.1 Genetic factors

There are several lines of evidence which suggest that there is a strong genetic component to diabetes in the elderly, although the specific genes responsible have yet to be defined [2]. If you have a family history of type 2 diabetes, you are much more likely to develop the disease as you age [3]. Diabetes is much more common in the elderly in certain ethnic groups [4], while the likelihood that an elderly identical twin will develop diabetes if their sibling is affected is over 80%. Even in elderly identical twins discordant for type 2 diabetes, the unaffected siblings clearly have evidence of abnormal glucose metabolism [5].

1.1.2 Age-related changes in carbohydrate metabolism

The progressive alterations in glucose metabolism that occur with age explain why genetically susceptible older individuals may not develop diabetes until late in life. Pathogenic mechanisms which contribute to the glucose intolerance of aging include alterations in glucose-induced insulin release and resistance to insulin-mediated glucose disposal [6]. Early investigations suggested that glucose-induced insulin release was normal in the elderly. However, more recent studies enrolling large numbers of carefully characterized healthy young and old subjects have demonstrated definable alterations in glucose-induced insulin release in the aged [6, 7]. Part of the reason for the decrease in insulin secretion is an impairment in islet mass and reduced β-cell proliferation [8]. In addition, the magnitude of the decrement in insulin secretion is more apparent in response to oral than to intravenous glucose [6]. This may be due, in part, to a decreased β-cell response to the incretin hormones (see below). As with many hormones, insulin is secreted in a pulsatile fashion. Normal aging is associated with subtle alterations in pulsatile insulin release, which further contribute to age-related changes in glucose metabolism [9]. Elevated levels of proinsulin, which suggest disordered insulin processing, predict the subsequent

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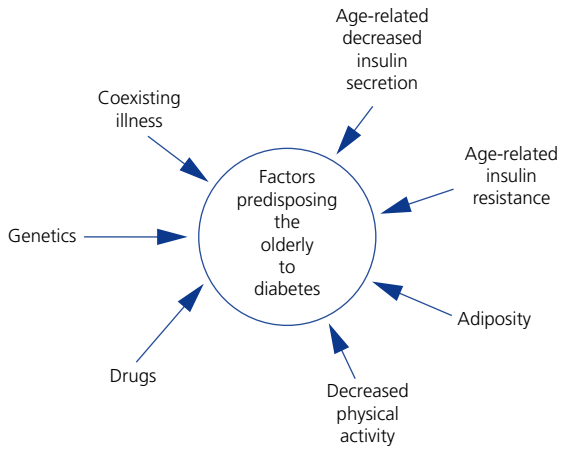

Figure 1.1 Factors that contribute to the high prevalence of diabetes in the elderly. Reproduced with permission from Halter, J.B., Carbohydrate metabolism, in: E.J. Masoro (ed.), *Handbook of Physiology, Volume on Aging*. New York, Oxford University Press Inc., 1995, p. 119.

development of type 2 diabetes in elderly subjects [10]. Thus, it is clear that alterations in glucose-induced insulin release are an important component of the changes in carbohydrate metabolism with aging. However, the most important pathogenic mechanism underlying the glucose intolerance of aging is resistance to insulin-mediated glucose disposal [2, 6, 11]. Debate persists as to whether the insulin resistance of the elderly is intrinsic to the aging process itself, or is the result of lifestyle factors commonly associated with aging. The consensus of opinion is that the aging process itself is the most important cause of insulin resistance, although lifestyle changes are clearly an important contributing factor. The molecular and cellular changes contributing to insulin resistance are detailed below.

1.1.3 Lifestyle and environmental factors

Despite the strong genetic component, it is abundantly clear that various environmental and lifestyle factors can increase or decrease the likelihood that a genetically susceptible individual will develop the disease in old age. Many older people have coexisting illnesses and take multiple drugs (e.g., thiazide diuretics, antipsychotic drugs), which can allow a latent abnormality in glucose metabolism to develop into full-blown diabetes [12, 13]. Obesity, especially with a central distribution of body fat, and a reduction in physical activity as well as functional decline occur progressively with aging, and these factors are associated with abnormal carbohydrate metabolism and diabetes in the elderly [2, 13–21].

The above information suggests that lifestyle modifications may be of value in the prevention of type 2 diabetes in the elderly, even in patients with a strong family history of the disease. Indeed, the Diabetes Prevention Program found that a combined lifestyle intervention consisting of weight loss and increased physical activity was effective in reducing the incidence of diabetes in elderly patients with impaired glucose tolerance [22].

1.2 Diet and diabetes in the elderly

Diabetes is more likely to develop in older patients who have a diet that is high in saturated fats and simple sugars, and low in complex carbohydrates [14, 23–25]. Moderate alcohol consumption may protect against diabetes in elderly women [26]. It has been suggested that deficiencies of trace elements or vitamins may contribute to the development or progression of diabetes in younger subjects, and it is increasingly recognized that the same may be true in the elderly [13, 23]. Elderly patients with diabetes have exaggerated free radical production, and administration of the antioxidant vitamins C and E to these patients improves both insulin action and metabolic control [27, 28]. Some epidemiologic studies have shown an association between low levels of vitamin D and diabetes in the elderly [29–32] but others have not [33]. To date, there have been no trials to test the hypothesis that treatment with vitamin D in elderly patients predisposed to diabetes will prevent its development. There is a correlation between increased intake of vitamin K and a reduced incidence of diabetes in the elderly [34]. Many elderly patients with diabetes are deficient in magnesium and zinc, and supplements of zinc and magnesium can improve glucose metabolism [35–37]. Increased dietary iron may be associated with an increased risk of diabetes in aged individuals [38]. Although chromium deficiency has been shown to cause abnormalities in glucose metabolism in animals and younger patients, there is no evidence to date that chromium supplements will improve glucose tolerance in the elderly. There is also no evidence that selenium deficiency is associated with an increased risk of diabetes in the elderly [39]. Persistent organic pollutants

and byproducts of plastics have been associated with diabetes in some studies [40, 41]. In summary, there is increasing evidence to suggest that dietary abnormalities or environmental factors may contribute to the pathogenesis of diabetes in the elderly, and that modifications of these parameters may be of therapeutic benefit.

1.3 Other factors

The presence of inflammation, as evidenced by elevated levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), cathepsin, and C-reactive protein (CRP), is associated with an increased risk of diabetes in the elderly [42–46]. Higher GGT levels, a marker of ongoing inflammation, are also associated with progression to diabetes in this age group [47]. Higher levels of adiponectin (an adipocytokine that increases insulin sensitivity) are associated with a reduced incidence of diabetes in the aged [48–52], whereas the opposite effect occurs with higher levels of fetuin-A, a protein that binds to the insulin receptor and inhibits insulin action. Sex steroid hormone levels also appear to be related to the development of diabetes in the elderly [53, 54]. In particular, higher testosterone levels in women and lower levels in men appear to be associated with an increased incidence of diabetes.

1.4 Metabolic alterations

The metabolic alterations which occur in middle-aged subjects with type 2 diabetes have been extensively characterized [1]. When compared to age- and weight-matched controls, both lean and obese middle-aged subjects have elevated fasting hepatic glucose production, a marked resistance to insulin-mediated glucose disposal, and a profound impairment in glucose-induced pancreatic insulin release.

Recently, metabolic factors have been characterized in lean and obese elderly patients with diabetes [55–58]. These studies have demonstrated some surprising differences in the metabolic profile between middle-aged and elderly subjects. In contrast to younger subjects, fasting hepatic glucose production is normal in both lean and obese elderly subjects (Figure 1.2). Similar to younger subjects, lean elderly patients have a profound

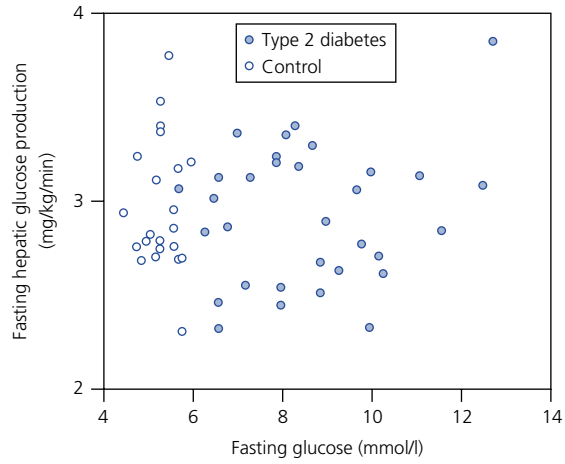

Figure 1.2 Fasting hepatic glucose production in relation to fasting glucose levels in healthy elderly controls and elderly patients with diabetes. Hepatic glucose production was measured by infusing radioactive glucose tracers.

impairment in pancreatic insulin secretion but, in contrast to the young, these patients have minimal resistance to insulin-mediated glucose disposal (Figures 1.3 and 1.4). In contradistinction to the young, obese elderly subjects have relatively preserved glucose-induced insulin secretion (see Figure 1.3), although pulsatile insulin secretion is clearly altered [8]. Similar to the young, however, these patients have a marked resistance to insulin-mediated glucose disposal (Figure 1.4). In summary, the principal defect in lean elderly subjects is impaired glucose-induced insulin release, while the principal defect in obese patients is resistance to insulin-mediated glucose disposal.

The ability of insulin to enhance blood flow is markedly reduced in obese, insulin-resistant older patients with diabetes (Figure 1.5) [57]. Insulin-mediated vasodilation is thought to account for about 30% of normal glucose disposal, presumably because it increases the delivery of insulin and glucose to muscle tissue. Indeed, it has been demonstrated that angiotensin-converting enzyme (ACE) inhibitors may improve insulin sensitivity in elderly patients with diabetes and hypertension [59]. This suggests that drugs which enhance muscle blood flow may prove to be valuable adjuncts in the future for the therapy of elderly patients with diabetes.

Autoimmune phenomena play a pivotal role in the β-cell failure that occurs in patients with type 1 diabetes [60]. It is increasingly recognized that a subset of

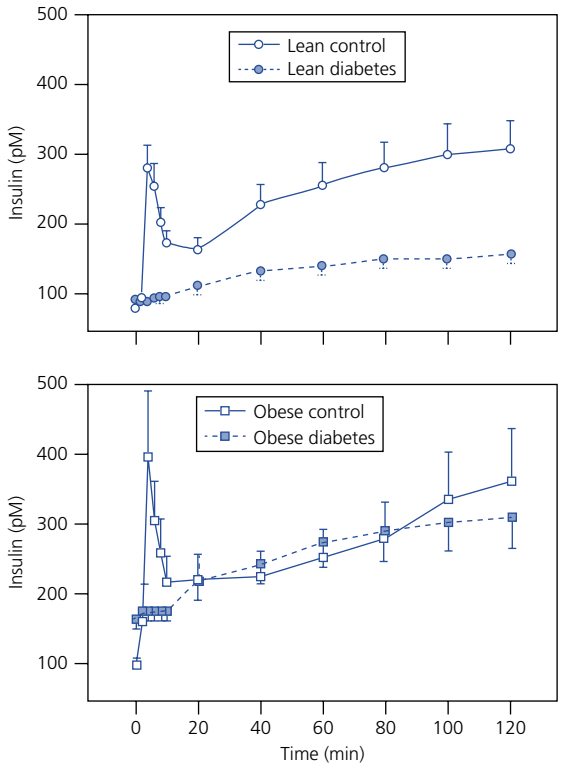

Figure 1.3 Glucose-induced insulin release in healthy elderly controls and elderly patients with diabetes. Insulin values were measured at glucose levels approximately 5 mmol/l above fasting levels.

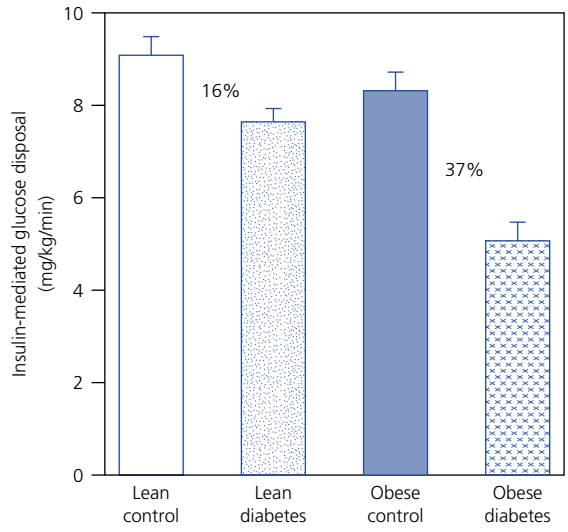

Figure 1.4 Insulin-mediated glucose disposal rates in healthy elderly controls and elderly patients with diabetes. Glucose disposal rates were measured utilizing the euglycemic clamp technique. In this technique, insulin is infused to achieve levels occurring after a meal, and glucose is infused simultaneously to prevent hypoglycemia.

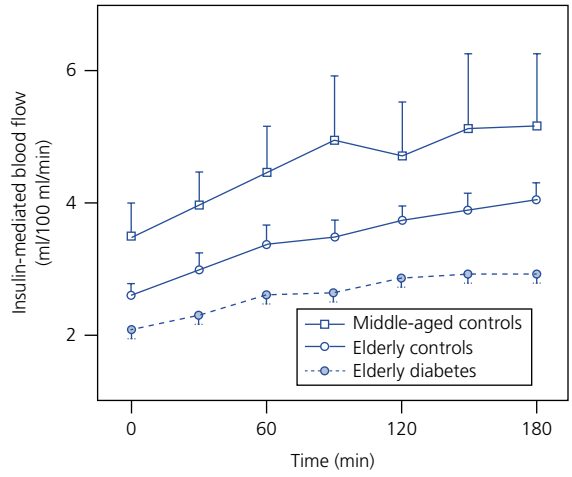

Figure 1.5 Insulin-mediated blood flow in obese middle-aged controls and obese elderly controls and patients with diabetes. Blood flow was measured in the calf during euglycemic clamp studies utilizing venous occlusion plethysmography.

middle-aged patients with type 2 diabetes have a form of diabetes that is characterized by β-cell failure, and these patients often have high titres of islet cell antibodies and antibodies to glutamic acid decarboxylase (GAD), similar to younger patients with type 1 diabetes. These patients are said to have latent autoimmune diabetes in adults (LADA) [61–64]. It is tempting to speculate that autoimmune phenomena contribute to the profound impairment in glucose-induced insulin secretion seen in lean older patients with type 2 diabetes. However, the clinical significance of elevated antibodies in the elderly is less certain. Some studies have found that elderly patients with diabetes who are positive for GAD have impaired β-cell function relative to controls without these antibodies, but others have not [65, 66]. It has been suggested that screening for auto-antibodies should be performed in elderly patients with impaired glucose tolerance (IGT) and newly diagnosed diabetes in order to help predict which patients will develop islet cell failure. Although this is a compelling idea, we should only begin widespread screening when randomized studies have demonstrated that early intervention will protect the β

cells and reduce the need for insulin therapy [63, 64]. Thus, it is unclear at present whether the measurement of autoimmune parameters can be used to predict future insulin requirements in the aged, or whether elderly patients with these abnormalities should be treated with therapies designed to modify autoimmune destruction of the pancreas.

Based on the above information, it is believed that the therapeutic approach to diabetes in the elderly should be different. In middle-aged patients, many endocrinologists recommend that patients be treated with drugs that both stimulate insulin secretion and improve insulin sensitivity, on the assumption that most patients have multiple metabolic problems. However, in lean elderly subjects the principal defect is an impairment in glucose-induced insulin secretion, and the main approach should be to administer secretogogues to stimulate insulin secretion, or to administer exogenous insulin. In obese elderly patients, the principal defect is insulin resistance; hence, patients should be treated initially with drugs that enhance insulin-mediated glucose disposal, such as metformin.

1.4.1 The incretin pathway

The enteroinsular axis refers to hormones released from the gut in response to nutrient ingestion that result in enhanced glucose-induced insulin release, known as the "incretin effect." The most important incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). When compared to younger controls, both basal and glucose-stimulated GIP and GLP-1 levels have been found to be unchanged or to be increased in healthy elderly subjects, and elderly patient with diabetes [67–70]. The level of dipeptidyl peptidase IV (DPIV), the enzyme that breaks down GIP and GLP-1, is progressively reduced with aging and diabetes. β-cell responses to GIP are reduced in normal elderly subjects and are absent in elderly patients with diabetes [71, 72]. In contrast, β-cell responses to GLP-1 are preserved in the elderly patient with diabetes [73]. These data suggest that GLP-1 and its analogues may prove to be useful therapeutic options in the elderly. This also suggests that agents which prevent the breakdown of GLP-1, such as DPIV inhibitors, may be less effective, although recent clinical trials do not support this hypothesis.

1.4.2 Glucose effectiveness or non-insulin-mediated glucose uptake

It has been recognized for many decades that insulin is an important hormone involved in the uptake of glucose into cells. It has also been demonstrated that glucose can stimulate its own uptake in the absence of insulin [74], an effect that is known as "glucose effectiveness" or non-insulin-mediated glucose uptake (NIMGU). Under fasting conditions, approximately 70% of glucose uptake occurs via glucose effectiveness, primarily in the central nervous system. After a meal, approximately 50% of glucose uptake in normal subjects occurs via NIMGU, with the bulk occurring in skeletal muscle. Because many middle-aged subjects with diabetes are insulin-resistant, it has been suggested that up to 80% of postprandial glucose uptake in these patients may occur via glucose effectiveness. At the present time it is uncertain whether defects in NIMGU contribute to elevated glucose levels in middle-aged patients with diabetes, as studies which have evaluated this parameter have provided inconsistent results.

In healthy elderly subjects glucose effectiveness is impaired during fasting, but is normal during hyperglycemia [75]. Elderly patients with diabetes have an even greater impairment in glucose effectiveness than healthy elderly subjects (Figure 1.6) [76]. Although the cause of

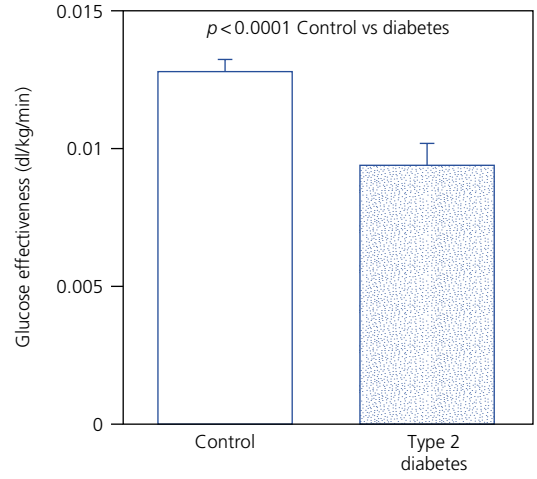

Figure 1.6 Glucose effectiveness in elderly controls and patients with diabetes. During these studies, insulin secretion was suppressed by infusing the somatostatin analogue octreotide. Glucose was then infused to assess glucose disposal in the absence of insulin.

this abnormality is uncertain, it may relate to a decreased ability of glucose to recruit glucose transporters to the cell surface.

In the future, this metabolic abnormality may prove to be of great therapeutic relevance to the elderly. In younger patients, exercise, anabolic steroids and a reduction in free fatty acid levels have been shown to enhance glucose effectiveness [74]. Since we have shown that the incretin hormone GLP-1 may enhance NIMGU in elderly patients with diabetes [77], it is possible that future therapies for the elderly may be directed not only at increasing insulin secretion and reversing insulin resistance, but also at enhancing glucose effectiveness.

1.5 Molecular biology studies

At present there is limited information available regarding molecular biological abnormalities in elderly patients with diabetes. The glucokinase gene controls the glucose sensor for the β cell, and defects in this gene could lead to the impairment in glucose-induced insulin secretion in lean elderly patients with diabetes. To date, evidence for mutations in this gene in the elderly is conflicting [78, 79].

In skeletal muscle, insulin binds to its receptor, resulting in activation of the insulin receptor tyrosine kinase. Activation of this enzyme sets in motion a cascade of intracellular events that results in the translocation of glucose transporters to the cell surface. In theory, a defect in any of these pathways could lead to insulin resistance. To date, these intracellular processes have been incompletely studied in elderly patients with diabetes, but the preliminary information suggests that while insulin receptor numbers and affinity are normal, the insulin receptor kinase activity may be defective [80]. Recent data have suggested that mitochondrial dysfunction contributes to insulin resistance in middle-aged patients with diabetes, and potentially also to impairments in glucose-induced insulin release [81]. Age-associated reductions in mitochondrial number and function, possibly due to cumulative damage by reactive oxygen species (ROS), predispose the elderly to ectopic lipid accumulation and insulin resistance in muscle and liver [2, 8, 82, 83]. Preserving mitochondrial function by reducing mitochondrial oxidative damage may be a therapeutic target for preventing an age-associated reduction in mitochondrial function, insulin resistance, and type 2 diabetes. Although normal aging is characterized by progressive mitochondrial dysfunction, to date no studies have been performed to assess mitochondrial function in elderly patients with diabetes [83]. Clearly, further studies are required to elucidate the subcellular defects that cause abnormal glucose metabolism in the elderly patient with diabetes.

1.6 Glucose counter-regulation

Numerous studies have demonstrated that elderly patients with diabetes, when compared to younger patients, have an increased frequency of severe or fatal hypoglycemia [13, 84, 85]. Hypoglycemia is the second most common cause of iatrogenic admission to the hospital in the elderly [86]. Asymptomatic hypoglycemia is very common and can be prolonged [87], and it is frequently associated with cardiac abnormalities [88]. Several studies have evaluated glucose counter-regulation in elderly subjects in an attempt to determine the cause of the increased frequency of hypoglycemia, and a number of important observations have emerged. Many elderly patients with diabetes have not been educated about the warning symptoms of hypoglycemia and as a result do not know how to interpret these symptoms when they occur [89].

The most important hormone in the defense against hypoglycemia in normal subjects is glucagon. If glucagon responses are deficient, epinephrine becomes important, and growth hormone and cortisol come into play if hypoglycemia is prolonged. The responses of both glucagon and growth hormone to hypoglycemia are impaired in healthy elderly subjects, and to an even greater extent in older patients with diabetes (Figure 1.7) [90], although the responses do not differ from middle-aged patients with diabetes [91]. Yet, even when they are educated about the symptoms of hypoglycemia, the elderly have a reduced awareness of the autonomic and neuroglycopenic warning symptoms at glucose levels that would elicit a marked response in younger subjects (bremer, meneilly). Finally, elderly patients have an impaired psychomotor performance during hypoglycemia [90, 91], which would prevent them from taking steps to return the blood glucose value to normal, even if they were aware that it was low. Thus, the increased frequency of hypoglycemia in the elderly is due to a

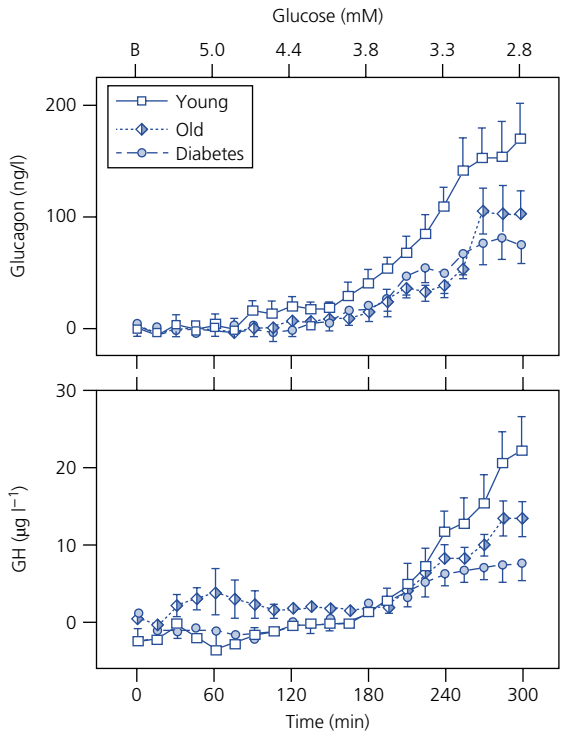

Figure 1.7 Glucagon and growth hormone (GH) responses to hypoglycemia in healthy young, healthy old, and elderly patients with diabetes. Controlled hypoglycemia was induced using the glucose clamp technique. Glucose values at which hormone levels were measured are shown on the top *x*-axis.

constellation of abnormalities, including reduced knowledge and awareness of the warning symptoms, decreased counter-regulatory hormone secretion, and altered psychomotor performance.

Levels of pancreatic polypeptide (PP) are elevated during hypoglycemia, and this response is mediated by the vagus nerve. The role of PP in normal glucose counter-regulation is uncertain, but in younger patients with diabetes a reduced PP response to hypoglycemia is an early marker of autonomic insufficiency. Although elderly patients with diabetes often have evidence of autonomic dysfunction, their PP responses to hypoglycemia are normal [92]. Thus, PP responses to hypoglycemia cannot be used to predict autonomic function in elderly patients.

Based on the above information, there are a number of interventions that can be proposed to prevent hypoglycemic events in the elderly. First, it would seem prudent to educate elderly patients about the warning symptoms of hypoglycemia so that they can appreciate them when they occur. Second, consideration should be given to the use of oral agents or insulin preparations that are associated with a lower frequency of hypoglycemic events in the elderly.

1.7 Conclusions

In summary, diabetes in older people is caused by a combination of genetic and environmental factors superimposed on the normal age-related changes in carbohydrate metabolism. The metabolic alterations that occur in elderly patients with diabetes appear to be distinct from those that occur in younger patients. As we gain a greater appreciation of the pathophysiological abnormalities that occur in the elderly, we hope to be able to develop a more focused approach to therapy in this age group. It is only in this way that we will be able to better cope with the epidemic of diabetes in the elderly that will befall us in the coming decades.

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CHAPTER 2
Type 1 diabetes in older age

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KEY MESSAGES

- Many older individuals with type 1 diabetes are highly disciplined and proactive in regards to their health and have lived for many years with a complex disease.
- Type 1 diabetes is increasingly being diagnosed in individuals aged 60 years and over.
- The primary management goal in older patients with type 1 disease remains the same as in younger patients, preventing acute and chronic complications associated with this disease, but there is the additional need to maintain functional status.
- The cautions used in treating aging adults with type 2 diabetes, in particular the focus on overall health goals and prevention of treatment-related complications (especially hypoglycemia), also remain important in those with type 1 disease.
- Co-morbidities commonly found in aging patients with type 2 diabetes, such as cognitive dysfunction, depression, physical disabilities, and polypharmacy, are also likely to coexist in older adults with type 1 disease.
- Insulin regimes can be advised according to the capability of patients to self-manage, the need for the individualized approach, and the need to attain sensible and realistic glucose targets.

2.1 Introduction

Traditionally, type 1 diabetes mellitus was thought to be a disease of children and younger adults. Over the past few decades understanding regarding the pathophysiology of diabetes has improved, leading to improvement in the management of the disease, as well as longer life expectancy for people with type 1 diabetes. As a result of the success in managing younger patients with type 1 diabetes, and the recognition that type 1 diabetes occurs in consistent numbers in all adult decades, healthcare providers have started managing a higher number of older adults with type 1 disease and these represent a small but unique population. These individuals are highly disciplined and proactive in regards to their health and have lived for many years with a complex disease. The exact prevalence of type 1 diabetes mellitus in this age group is not known, but is probably increasing as the population is aging. Based on the prevalence of type 1 diabetes in the younger population, and variable life expectancy in different parts of the world, the prevalence of type 1 diabetes in older adults is also likely to vary significantly among countries [1]. The differences in characteristics of older patients with type 1 and type 2 diabetes are noted in Table 2.1.

2.2 Goals in the management of type 1 diabetes in older adults

Although there is a paucity of data guiding the management of older persons with type 1 diabetes, small studies and expert analysis in the recent past have provided better understanding of how to manage the

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Table 2.1 Characteristics of older patients with type 1 or type 2 diabetes.

Characteristic	Type 1 diabetes	Type 2 diabetes
Duration of disease	Long	Shorter
Complexity of diabetes treatment regimen	Moderate to complex	Low complexity in majority of patients High complexity of associated co-morbidity treatment
Risk of hypoglycemia	High	High only for patients on insulin or sulfonylurea
Fear of hypoglycemia	Low	Usually high except when cognitive dysfunction is present
Comfort with performing self-care activities	High	Variable

aging population with type 2 diabetes (http://www.idf.org/guidelines/managing-older-people-type-2-diabetes) [2–4].

As patients with type 1 diabetes mellitus age, they face additional challenges based on the presence of coexisting medical conditions, which may interfere with the self-care they have performed for many decades. Changes in their social and functional environment may also interfere with their self-care abilities. Overall, as in older patients with type 2 diabetes, the primary management goal in older patients with type 1 disease remains the same as in younger patients, preventing acute and chronic complications associated with this disease, but there is the additional need to maintain functional status. Similarly, the cautions used in treating aging adults with type 2, in particular the focus on overall health goals and prevention of treatment-related complications (especially hypoglycemia), also remain important in those with type 1 disease.

One major difference seen between older adults with type 2 diabetes and those with type 1 diabetes is the discipline they have maintained over many decades to successfully manage their diabetes and keep glycemic control in a tight range. This behavior is typically deeply rooted. However, as patients with type 1 diabetes age, they also develop diabetes-related and diabetes-unrelated co-morbid conditions, functional decline, and the need for caregiver support. Although many older adults with type 1 diabetes continue to successfully manage their diabetes, the complex interaction with additional conditions may interfere with their ability to continue aiming for strict glycemic control and execute routine tasks previously performed for decades, such as rigorous glucose monitoring, complex insulin dose management, pump and continuous glucose monitoring operation, and maintaining dietary compliance. It is important to observe these patients closely for warning signs of decompensation such as coping difficulties or multiple errors in medications/insulin regimen, which may manifest as a change in diabetes control with frequent hypoglycemia or hyperglycemia. Careful discussion regarding risks and benefits of tight control needs to be undertaken at that point to avoid catastrophic consequences of hypoglycemia, such as traumatic falls. We have indicated in Table 2.2 a plan for insulin therapy according to the health and functional status of older people with type 1 diabetes.

2.3 Complications and co-morbidities

Several observational studies have followed patients with type 1 diabetes as they age and have reported the rate of complications. A cross-sectional observational study of over 350 patients with type 1 diabetes mellitus for a duration of >50 years in the USA reported that glycemic control (HbA1c) was not associated with the risk of complications in this population [5]. This long-surviving population also had very few microvascular and macrovascular complications, suggesting that they may have protective factors against diabetes complications. More studies are needed to understand the factors that might be responsible for this protection. Another study analyzed data from 350 diabetes centers treating over 64,000 patients with type 1 diabetes in Germany [6]. This analysis showed that older patients with type 1 diabetes (>60 years of age) had a higher risk of both macrovascular and microvascular complications compared to their younger counterparts. This older cohort also had lower HbA1c levels (7.6% vs 8.3%) and almost

Table 2.2 Therapy approach and glycemic targets for type 1 diabetes in older people.

Functional category	Focus of management	Fasting and preprandial glucose range (mmol/l)	HbA1c target % (mmol/mol)	Insulin regime
Robust, independent	Disease process and minimize vascular disease	7.0–8.0	7.0–7.5% (53–59)	Basal insulin (e.g., glargine or detemir) plus bolus insulin with meals Alternatively twice daily premixed (biphasic) insulin *Some patients with long-standing type 1 diabetes may still be prepared to continue pump therapy*
Frail, dependent	Maintenance of function	7.5–10.0	Up to 8.5% (70)	Twice daily premixed (biphasic) insulin or basal insulin once a day using long-acting insulin (NPH, glargine or detemir)
Dementia, dependent	Prevent functional deterioration and maintain quality of life	7.5–10.0	Up to 8.5% (70)	Twice daily premixed (biphasic) insulin or basal insulin once a day using long-acting insulin (NPH, glargine or detemir)
End of life	Palliative care and avoidance of hospital admission; reduce glucose monitoring	No specific target range; avoid symptoms and minimize hypoglycemia	No specific target; avoid symptomatic hyperglycemia and minimize hypoglycemia	Basal insulin once a day using long-acting insulin (NPH, glargine or detemir) if appropriate

double the risk of hypoglycemia compared with the younger cohort. Such observational data underscores the importance of individualizing glycemic goals as well as treatment strategies in older patients with type 1 diabetes.

Co-morbidities commonly found in aging patients with type 2 diabetes, such as cognitive dysfunction, depression, physical disabilities, and polypharmacy, are also likely to coexist in older adults with type 1 disease. Recently, much attention has focused on the high risk of cognitive dysfunction, as it presents a major barrier in performing self-care [7]. Several studies have shown a link between type 2 diabetes and dementia, and the association is thought to be bidirectional [8, 9]. However, there are fewer studies evaluating type 1 diabetes and neurocognitive disorders in older adults. One study evaluated the volume and severity of white matter hyper-intensities in middle-aged (mean age 50 years) patients with childhood-onset type 1 diabetes and compared them with age-matched controls without diabetes [10]. The results showed that patients with type 1 disease had an earlier presentation of clinically relevant white matter hyper-intensities associated with slower information processing compared to controls. A small study assessed the levels of circulating biomarkers in cerebrospinal fluid (CSF) of middle-aged patients with type 1 diabetes and compared them to age-matched controls [11]. The researchers found higher levels of biomarkers of Alzheimer's disease, including phosphorylated tau, beta-amyloid 42, and a soluble form of low-density lipoprotein receptor-related protein (sLRP1) in CSF of patients with type 1 disease compared to the controls.

Other population-based studies have evaluated the associations between cognitive dysfunction and diabetes. A recent study evaluated 12-year follow-up data on people >60 years of age belonging to a large US health system. They found 230 patients with type 1 diabetes out of over 490,000 patients on the database. The results showed that older adults with type 1 diabetes were 83% more likely to develop dementia compared with those without the disease [12]. Another prospective study also evaluated cognitive function in 200 patients over the age of 60 years with type 1 diabetes [13]. The authors found that 36–44% of the study patients had cognitive dysfunction as measured by the

Montreal Cognitive Assessment (MOCA) tool (available at http://www.mocatest.org) and the trails-making test, respectively. A meta-analysis performed on 33 studies evaluated cognitive dysfunction in patients with type 1 diabetes [14]. The results of the study showed impairment in certain domains of cognitive function, such as mental speed and mental flexibilities. In this study, learning and memory were spared. This type of executive dysfunction is important for self-care behaviors and may lead to errors when complex coping skills are needed. However, this area still needs more investigation, as seen by other small studies reporting variable results. A small longitudinal study that followed 36 patients with type 1 diabetes (mean age 60 ± 6 years; median follow-up 4.1 years) did not show any greater cognitive decline in individuals with type 1 diabetes compared to age-matched controls [15]. However, in this study the subgroup with one or more cardiovascular or hypoglycemic events was found to be more likely to develop cognitive decline. Thus, the data linking cognitive dysfunction to type 1 diabetes are not as robust as those linking to type 2 diabetes. Nonetheless, aging independently also increases the risk of cognitive dysfunction and thus screening for subtle cognitive/executive dysfunction is important in all older patients with diabetes due to its impact on self-care abilities.

The relationship between diabetes and depression has been studied extensively. Similar to cognitive dysfunction, the association between diabetes and depression is thought to be bidirectional. The prevalence of depression in type 1 diabetes is difficult to assess due to the different methods used by different epidemiological studies with sometimes conflicting results. A meta-analysis evaluating the cross-sectional prevalence of clinical depression in patients with type 1 diabetes found inadequate evidence to conclude that the prevalence of depression is different in adult patients with type 1 diabetes (ages 21–43 years) compared to the general population [16]. This study did not include any older adults. Other smaller studies have shown an association between depression in adults with type 1 diabetes and metabolic syndrome [17] and subclinical carotid atherosclerosis in men [18]. Depression in older adults with type 2 diabetes has shown associations with poor glycemic control, decreased adherence to treatment strategies, increased functional disability, and mortality [19–21]. However, studies evaluating these associations in older patients with type 1 diabetes are lacking. Nonetheless, it is important to be aware of the relationship between diabetes, depression, and self-care abilities.

Polypharmacy is a challenging aspect of caring for older adults with multiple chronic diseases. Although complex regimens are generally avoided in older patients with type 2 diabetes, patients with type 1 diabetes frequently need complex insulin regimens to maintain good glycemic control. In general, older patients with both type 1 and type 2 diabetes need more medications to control cardiovascular risk factors associated with diabetes and manage other non-diabetes-related co-morbidities. Polypharmacy is found to increase the risk of non-adherence, drug–drug interactions, side effects, and errors leading to catastrophic consequences [22, 23]. In addition, multiple consultants and lack of coordination of care amongst them can lead to further errors. The general principle of medication reconciliation at each visit is an important part of managing older patients with type 1 diabetes.

Aging and its impact on overall physical function, health status, vision, hearing, chronic pain, and falls leads to high risks of loss of independence and the need for more caregiver support [24, 25]. As many of the barriers to optimal diabetes management develop gradually with subtle presentations, it is important to periodically assess older type 1 diabetes mellitus individuals for physical, social, and emotional/cognitive dysfunctions.

2.4 Hypoglycemia

Risk of hypoglycemia is the primary consideration when establishing glycemic goals in all older adults. In this population, the benefits of tight glycemic control are limited, while the immediate consequences of hypoglycemia can be devastating and may include cardiac and cerebrovascular events, progression of dementia, injurious falls, emergency department visits, and hospitalizations [26–28]. The decline in overall functioning may even lead to institutionalization with unacceptable decline in quality of life. Although most of the findings are in older adults with type 2 diabetes and have not been replicated in patients with type 1 diabetes specifically, the risk of hypoglycemia increases with longer duration of the disease, treatment with insulin, and high complexity of the treatment regimen, all of which are more common in type 1 patients [29, 30]. In addition, many co-morbidities associated with poor

outcomes are likely to be age dependent and may affect older patients with both type 1 and type 2 disease. One difference frequently seen between older adults with type 2 and type 1 diabetes is that many older patients with type 2 diabetes are afraid of the adverse effects of hypoglycemia (e.g., falling and confusion) and over-treat lows, leading to widely fluctuating blood glucose readings. Paradoxically, many older adults with type1 diabetes are less concerned about hypoglycemic risks as they are accustomed to them, which leads to frequent episodes that are not managed well. In these older patients, appropriate and repeated education is needed as the hypoglycemic consequences may be more deleterious than those of hyperglycemia.

Most experts recommend a liberal goal for HbA1c to avoid hypoglycemia in vulnerable older patients with type 1 and type 2 diabetes. It is important to remember that higher HbA1c values in insulin-treated patients frequently suggest wide fluctuations of glucose levels and do not reflect lower risk of hypoglycemia [31]. Simplified strategies that match older patients' coping abilities are the best way to prevent hypoglycemia [32].

2.5 Multidisciplinary team approach

It has been well established that optimal diabetes management in all patients requires input from a team that consists of an endocrinologist, a diabetes-educator, a nutritionist, an exercise physiologist, and a psychologist. Older patients with type 1 diabetes may benefit from additional services beyond the traditional teams, such as clinical pharmacists, physical and occupational therapists, and rehabilitation services that take into account clinical, functional, and psychosocial diversity [33]. Caregivers, both formal (such as visiting nurses) and informal (family members or friends), also are an important part of the team caring for older adults with type 1 diabetes who are not able to perform self-care. Diabetes education for patients and caregivers, as well as treatment strategies, need to be flexible since they frequently change due to new obstacles or a decline in the individual's support structure. Resources such as visiting nurses and physical therapists might be available for housebound patients or post hospitalization for a short time, but delirium and deconditioning may last longer in frail type 1 diabetes mellitus patients. These patients may need a simplified insulin regimen and more caregiver support for a variable time. Personal and community resources are important, especially for patients with type 1 diabetes who are living alone, and these resources may dictate how the patient can be managed.

2.6 Long-term care

The prevalence of type 1 diabetes in long-term care facilities is not currently known, but with longer life expectancy we are bound to see an increasing number of older patients with type 1 disease in long-term care settings. Most published guidelines describing the principles of diabetes management in nursing homes are focused on the management of type 2 diabetes [34, 35]. It is important to educate long-term care facility staff members on diabetes management as they become the primary caregiver for the patients admitted there and perform most of the "self-care" for patients who are not able to perform this themselves anymore. The education should include the unique challenges facing patients with type 1 diabetes, as compared to commonly seen type 2 diabetes, an overview of the different insulins, interaction between insulin and carbohydrate content of meals, and hypoglycemia recognition and treatment.

2.7 Conclusion

Older adults with type 1 diabetes are a unique population, and are often proactive in their approach to their health care. These patients have mastered their diabetes management and typically feel strongly about controlling their hyperglycemia tightly. Typically, the role of the provider is to continue to support the patients in their effort to manage their diabetes. On the other hand, they do develop age-related impairments and co-morbidities that may interfere with complex management. With increasing functional disability and difficulty performing self-care, there is a high risk of errors in insulin dosing, meal planning or insulin/meal timing. These errors can result in wide glucose fluctuations and lead to great frustration on the part of the patients and caregivers. It is common to see frequent hypoglycemic episodes in older patients with type 1 diabetes who are not concerned about the repercussions, as they have had these episodes since childhood.

Subtle executive dysfunction makes it difficult for patients to change behaviors that have been rooted for many decades. Repeated education for patients and caregivers, and patience on the part of medical providers, is needed for successful aging and the best possible quality of life, in addition to good diabetes care.

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CHAPTER 3
Preventative strategies

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KEY MESSAGES

- All regions of the world are experiencing a rapid growth in the prevalence of diabetes but the epicenter of the diabetes epidemic is currently South-East Asia, India, and China.
- A key factor for the rapid increase in the prevalence of diabetes is the aging of the population in most parts of the world. In the USA, 26% of people 65 years or older have either diagnosed or undiagnosed diabetes.
- Findings support the conclusion that the preferred approach to diabetes prevention in an older population should be to implement a program of lifestyle modification that emphasizes eating a healthy diet, achieving significant weight loss, and increasing the daily amount of physical exercise.
- Major efforts are underway in the USA, as well as in other countries, to educate the population about the importance of eating a healthy diet, preventing or reducing obesity, and achieving adequate physical exercise with the goal of decreasing the incidence of diabetes and its long-term complications.

3.1 Introduction

The worldwide prevalence of diabetes continues to increase rapidly and in 2014 it was estimated to be 387 million people, with more than 90% having type 2 diabetes. Furthermore, it is now estimated that by 2035 the prevalence will reach 592 million people, more than a 50% increase in only 21 years [1]. The absolute numbers and percentages of the population with diabetes and the projected rates of increase vary considerably in different parts of the world, often reflecting multiple factors that include the size of the population, socioeconomic growth and associated changes in diet and physical activity, aging of the population, and genetic susceptibility. While all regions of the world are experiencing this rapid growth in the prevalence of diabetes, the epicenter of the diabetes epidemic is currently in South-East Asia, India, and China.

A major factor in the increasing prevalence of diabetes is its association with obesity, particularly central or intra-abdominal obesity [2, 3]. The age-adjusted relative risk for type 2 diabetes is low in people with a body mass index (BMI) ≤25, but increases rapidly in both men and women who are overweight (BMI 25–30) or obese (BMI >30). When the BMI is ≥35 the age-adjusted relative risk for type 2 diabetes exceeds 40% in men and 90% in women. This association is now frequently described as a dual epidemic of obesity and diabetes. Currently, 65% of Americans are overweight, 32% are obese, and 34% meet the Adult Treatment Panel (ATP) III criteria for having metabolic syndrome [4, 5], all of which are risk factors for the development of diabetes. In addition, many studies have demonstrated that impaired glucose metabolism, manifested by either impaired fasting glucose or impaired glucose tolerance, is a significant risk factor for progression to overt diabetes [6]. This has led to the use of the term "pre-diabetes" for these conditions.

Another key reason for the rapid increase in the prevalence of diabetes is the aging of the population in most

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parts of the world. In the USA, 26% of people 65 years or older have either diagnosed or undiagnosed diabetes. This represents approximately 11 million people or 39% of the total adult population with diabetes [4]. Thus, diabetes in the aging population is now recognized as a major health problem and preventative strategies are a major priority in health care.

3.2 Diabetes and cardiovascular disease

In people with type 2 diabetes, cardiovascular disease (CVD) is a major cause of morbidity and mortality. For example, in the Framingham study a 30-year follow-up of a cohort of people age 35–64 found that men had a two- to three-fold increased risk of coronary heart disease (CHD) and total CVD, and women had a four-fold increased risk of CHD and total CVD when compared to people without diabetes [7]. In addition, many studies have found that people with impaired glucose metabolism (pre-diabetes) are also at increased risk for developing CVD and cardiac mortality [8]. More recently, metabolic syndrome has become recognized as an independent risk factor for the development of diabetes, in addition to being a risk factor for CVD [9]. Thus preventative strategies have generally focused on treating high-risk individuals who have pre-diabetes or other significant risk factors such as obesity or metabolic syndrome.

3.3 Trials to prevent or delay progression from impaired glucose tolerance to diabetes

There are now a large number of clinical trials that have been conducted to examine the effectiveness of various treatment regimens to prevent or delay the development of diabetes in people who are at high risk because they have impaired glucose tolerance (IGT). These can be divided into those that have focused on programs of intensive lifestyle modification (ILS), usually involving dietary restriction, weight loss, and increased physical exercise [10–15], and those that have used medications, particularly classes of drugs that are commonly used to treat people with type 2 diabetes (Table 3.1) [16–24]. These include trials using insulin secretogogues, metformin, alpha-glucosidase inhibitors, thiazolidinediones, long-acting insulin preparations, and weight-loss medications. While many of these medications are very effective in decreasing the risk of progression to diabetes, many also have significant undesirable side effects which limit their use. In general, sulfonylureas and meglitazones are not effective in preventing diabetes, whereas metformin, alpha-glucosidase inhibitors, and thiazolidinediones are effective. The relative risk reductions (RRRs) with the alpha-glucosidase inhibitors acarbose and voglibose have ranged from 25% in the STOP-NIDDM study [17] to 40% with voglibose [20], the RRR with metformin in the Diabetes Prevention Program [25] was 31% and the RRRs with troglitazone in the TRIPOD Study [16], rosiglitazone in the DREAM Study [19], and pioglitazone in the ACT NOW Study [18] were between 55 and 80%. In the ORIGIN Trial, which used glargine insulin, the RRR was 28% [23]. Thus, use of these medications to treat people at increased risk of developing type 2 diabetes because they have IGT could be expected to reduce the risk of progression to diabetes. However, each class of medication has significant side effects and potential safety issues. Metformin is generally considered to be extremely safe, but some people develop gastrointestinal side effects that limit their ability to take a sufficient dose or remain on treatment for long periods of time. The gastrointestinal side effects of the α-glucosidase inhibitors are often limiting for people and they are most effective in selected populations who consume a diet that is high in complex carbohydrates. The currently available thiazolidinediones rosiglitazone and pioglitazone have many potentially limiting side effects including fluid retention, weight gain, an increased risk of congestive heart failure, and an increased risk of fractures. Finally, treatment with insulin preparations, such as glargine insulin, are associated with weight gain and an increased risk of hypoglycemia. In addition, few of the studies using medications have included a significant number of subjects age 65 or older, so the effectiveness of the medications in an elderly population is not well characterized. One exception is the Diabetes Prevention Program (DPP) in the USA in which it was found that metformin was much less effective than a lifestyle intervention program in older subjects aged 60–85 years [10]. Figure 3.1 shows the diabetes incidence rates in the DPP in subjects, subdivided by age and

Table 3.1 Summary of results of major randomized controlled trials of medications and lifestyle interventions to prevent the development of type 2 diabetes mellitus in people with impaired glucose tolerance.

Trials [ref no.]	Subjects	Intervention	Median duration (years)	RRR (%)
Malmo [11]	181	Lifestyle	6	NA
Da Qing [13]	577	Diet only	6	48
		Exercise only	41	
		Diet + exercise	46	
Finnish DPS [15]	522	Lifestyle	3.2	58
DPP [26]	3234	Metformin 1700 mg/day	2.8	31
		Lifestyle	2.8	58
[28]	585	Troglitazone 400 mg/day	0.9	75
Japanese study [12]	458	Lifestyle	4	67
Indian study [14]	531	Lifestyle only	2.5	29
		Metformin 500 mg/day	26	
		Lifestyle + metformin	28	
STOP-NIDDM [17]	1429	Acarbose 100 mg tid	3.3	25
Voglibose [12]	1780	Voglibose 0.2 mg tid	1	40
TRIPOD [4]	266	Troglitazone 400 mg/day	2.5	55
DREAM study [19]	5269	Rosiglitazone 8 mg/day	3	60
		Ramapril	NS	
ACT NOW [18]	602	Pioglitazone 45 mg/day	2.4	72
NAVIGATOR [33]	9306	Nateglinide to 60 mg tid	5	NS
		Valsartan to 160 mg/day	14	
ORIGIN [25]	1456	Glargine insulin	6.2	28
XENDOS [24]	3305	Orlistat 120 mg tid	4	37

RRR, relative risk reduction compared to randomized control subjects.

treatment group. These findings support the conclusion that the preferred approach to diabetes prevention in an older population should be to implement a program of lifestyle modification that emphasizes eating a healthy diet, achieving significant weight loss, and increasing the daily amount of physical exercise.

3.4 Diabetes prevention trials using lifestyle modification programs

Several clinical trials of the effects of weight reduction and increased physical activity to reduce the risk of developing diabetes in high-risk populations have been

Figure 3.1 Diabetes incidence by age group in the Diabetes Prevention Program. Adapted from The Diabetes Prevention Program Research Group, *et al.* J Gerontol A Biol Sci Med Sci 2006; 61: 1075–81 with permission.

conducted [10–15]. Three of these trials are particularly noteworthy because of their long-term follow-up of the participants: the Da Qing study conducted in China, the Finnish Diabetes Prevention Study (DPS), and the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS) conducted in the USA.

3.5 The Da Qing study

One of the first major clinical trials to study the effects of dietary modification, weight loss, and increased physical activity to prevent the progression to diabetes in people with documented IGT was the Da Qing trial [13]. In this study 577 adult men and women with IGT, mean age 45 ± 9 years, who were being followed in 33 community clinics in Da Qing, China, were divided into one of four treatment groups depending on the clinic they attended. One group of clinics served as the study control, where the subjects received standard medical care without a defined program of lifestyle intervention, and the other three groups were assigned by clinic to a program of dietary modification alone, an exercise program alone or a combined diet plus exercise program. The dietary intervention focused on increasing the use of vegetables and complex carbohydrates in the diet, decreasing the use of alcohol, and losing weight if the BMI was >25. The exercise program involved increasing the activities of daily living and doing moderate intensity exercise equivalent to brisk walking for at least 20 min a day. The combined diet and exercise group was instructed to follow both the dietary and exercise interventions. The participants were followed for 6 years during the active intervention phase of the study and received an oral glucose tolerance test (OGTT) every 2 years to determine the incidence of diabetes. At the conclusion of the initial 6-year study period the incidence of conversion to diabetes was 68% in the control subjects and was significantly lower in all three intervention groups, being 48%, 41%, and 46% in the diet only, exercise only, and combined diet plus exercise groups, respectively. This represents a 30–40% RRR with either diet or exercise alone and no apparent added benefit of combing both the diet and exercise programs.

Since completion of the main study, there has been continued follow-up of the participants for conversion to diabetes and for cardiovascular and all-cause mortality [26]. After 23 years, complete data on mortality were available in 94% of subjects and 99% contributed data for analysis. The incidence of diabetes was 72.6% in the intervention groups compared to 89.9% in the controls ($p = 0.001$) and the incidence of CVD mortality was 11.9% vs 19.6% ($p = 0.033$), respectively. Thus, the intervention programs involving diet and physical exercise significantly reduced both the development of diabetes and CVD mortality, supporting the long-term clinical benefits of this approach to treating pre-diabetes. The Da Qing study has not presented data on specific age groups, but the average age of the study population

is now greater than 65 and the beneficial results of the previous lifestyle modification programs are still clearly apparent in decreasing the incidence of diabetes, cardiovascular disease, and all-cause mortality in this aging population.

3.6 The Finnish Diabetes Prevention Study

The Finnish Diabetes Prevention Study is another landmark study that examined the effects of a program of intensive lifestyle modification in 522 middle-aged, overweight men and women with IGT [15]. In this study, which started recruitment in 1993, the mean age of participants was 55 ± 7 years and the mean BMI was 31 kg/m^2. The participants were randomly assigned to either a control group or an intervention group in which participants were given individual counseling aimed at reducing body weight by reducing total calorie intake, specifically by decreasing the intake of total and saturated fat and increasing the intake of dietary fiber, and by increasing moderate intensity physical exercise equivalent to brisk walking for at least 4 h each week. An OGTT was done annually and a diagnosis of diabetes was confirmed by a second test. After a mean follow-up of 3.2 years, the cumulative probability of remaining free of diabetes was significantly increased in the lifestyle intervention group, with an RRR of 58% compared to the control group [15]. In this study, the RRR in the intervention group was found to be directly related to the lifestyle changes that were achieved. For example, participants who lost 5% or more of their body weight had a 74% RRR and participants who exceeded the recommended 4 h of exercise/week had an 80% RRR.

As in the Da Qing study, long-term follow-up of the participants in the Finnish Diabetes Prevention Study has demonstrated the continued benefits of the lifestyle modification program. After a median of 3 years of follow-up, there was still an overall 43% RRR for development of diabetes in the intervention group compared to the control group [27]. Further follow-up, conducted a median of 9 years after completion of the active intervention phase of the study and 13 years after the baseline evaluations, revealed that the adjusted hazard ratio (HR) for developing diabetes was 0.614 ($p < 0.001$) for the lifestyle intervention group compared to the control group. The corresponding HR during the post-intervention follow-up was also significantly decreased, being 0.672 ($p = 0.023$) [28]. Thus, there was continued reduction in the risk of developing diabetes for at least 9 years after completing the study in those participants who had participated in the lifestyle intervention program. In addition, these subjects maintained lower body weight, lower glucose levels, and a healthier diet compared to the control group participants. As in the Da Qing study, no data are presented on specific age groups at randomization, but the mean age at follow-up is now >65 years.

3.7 The Diabetes Prevention Program/ Diabetes Prevention Program Outcomes Study

The DPP/DPPOS is the largest study to date to examine the efficacy of a lifestyle modification program to prevent or delay the development of type 2 diabetes in adults with IGT [25]. It is being conducted in 27 centers in the USA and for the DPP phase enrolled 3234 people, mean age 51 ± 10 years, mean BMI 34 kg/m^2, 68% women and good representation of the various racial and ethnic groups in the US population. Subjects were randomized to one of three treatment groups: a placebo-treated control group ($n = 1082$), a group taking metformin, 850 mg twice daily ($n = 1073$), and a group given a program of intensive lifestyle modification (ILS) ($n = 1079$) that focused on reducing total and saturated dietary fat, increasing dietary fiber, and increasing moderate intensity physical exercise for at least 150 min per week. The overall goal of the ILS program was to achieve and maintain a weight loss of 7% of initial body weight. The original study design also included a fourth group of subjects who were treated with troglitazone, 400 mg/day, but this treatment was discontinued before recruitment was completed when it was found that troglitazone was associated with a significant risk of liver toxicity [29].

In the ILS group, the weight-loss goal was achieved within the first 6 months and maintained for at least 1 year, following which there was some gradual increase in body weight, so that by the end of the study the mean weight loss was approximately 4% of the original body weight. The exercise goal was exceeded, averaging approximately 215 min per week, and this was

maintained throughout the DPP phase of the study. Compliance with taking metformin was also excellent during the DPP. The participants had OGTTs done annually and fasting glucose measured at 6-month intervals. Conversion to diabetes was confirmed by a second test. This phase of the study was terminated after a mean duration of treatment for 2.8 years because the results were so positive. The control group had a conversion rate to diabetes of 11.0 cases per 100 person-years. The conversion rate was 7.8 cases per 100 person-years in the metformin-treated group and 4.8 cases per 100 person-years in the ILS group, representing 31% and 58% reductions in RRR, respectively [25]. Because of these positive results and the clear superiority of the ILS program to prevent or delay the conversion to diabetes, the DPP phase of the study was stopped early. The placebo control and metformin groups were unblinded, metformin was stopped for a short time and then restarted in an unblinded fashion, and both groups were provided with a 16-week course in the ILS program. The so-called "bridge period" lasted approximately 1 year and then the DPPOS long-term follow-up phase of the study was started. The metformin group was asked to continue to take metformin, the ILS group was asked to continue the diet and exercise program, and the control subjects were asked to continue as the control group. The response was excellent, with 88% of subjects ($n=2766$) continuing in the long-term follow-up phase [30].

In the original DPP study there were no differences in the efficacy of the metformin or ILS interventions in the various racial and ethnic groups, and no differences between men and women. The effectiveness of metformin was greatest in the younger age group (25–44 years), being equivalent to that of the ILS program, and, conversely, the ILS program was most effective in the older age group (60–85 years) [10]. Metformin was also most effective in more obese subjects with a BMI >36 and least effective in those with a BMI <30. The effectiveness of the ILS program was related to the amount of weight lost and to improvements in both insulin sensitivity and secretion [31, 32].

The DPP also evaluated the effects of the metformin and ILS interventions on CVD risk factors and components of the metabolic syndrome [33–35]. At the time of randomization, 53% of the subjects had the metabolic syndrome using the original ATP III criteria. There were no differences in the prevalence of the metabolic syndrome by gender or age group, but the prevalence was lower in the Asian (41%) and highest in the Caucasian (57%) subgroups. The lower prevalence in the Asians is partially explained by the fact that no adjustment was made in the waist circumference criteria in this population. There were also some racial/ethnic differences in the prevalence of the individual components of the metabolic syndrome, similar to those observed in other studies.

In subjects who did not have the metabolic syndrome at baseline, 53% of those in the placebo group had developed it after 3 years and treatment with metformin reduced the RRR of developing metabolic syndrome by 17% and the ILS program reduced the RRR by 41%. Furthermore, the ILS program resulted in the reversal of the metabolic syndrome in 38% of those who met the ATP III criteria at randomization. Thus, the ILS program was effective in both preventing the development of the metabolic syndrome in those who did not have it at baseline and reversing it in those who did [34]. In addition, the ILS program was effective in improving several well-established CVD risk factors. Hypertension was present in 30% of participants at baseline and its prevalence increased in both the control and metformin groups after 3 years, but decreased significantly in the ILS group. Triglycerides decreased in all three groups, but significantly more in the ILS group, and ILS was associated with an increase in serum HDL-C and reduction in the small, dense LDL-C fraction, as well as with less use of medications to treat hypertension and dyslipidemia [34]. In addition, after 1 year of intervention, hsCRP levels were decreased by 7–14% in the metformin group and by 29–33% in the ILS group [33]. Thus, the ILS program was associated with significant improvements in several of the measured CVD risk factors and was more effective than metformin in this regard.

In another analysis, the association of the metabolic syndrome and its various components with the progression to diabetes was examined [36]. The key findings were that the metabolic syndrome, and particularly increased fasting glucose and triglyceride concentrations, were significant predictive factors for the development of diabetes in the DPP. Greater waist circumference was also predictive in the placebo control and lifestyle groups, but not in the metformin group. Treatment-associated improvements in waist circumference and in HDL-C concentrations were also associated with decreased risk of developing diabetes.

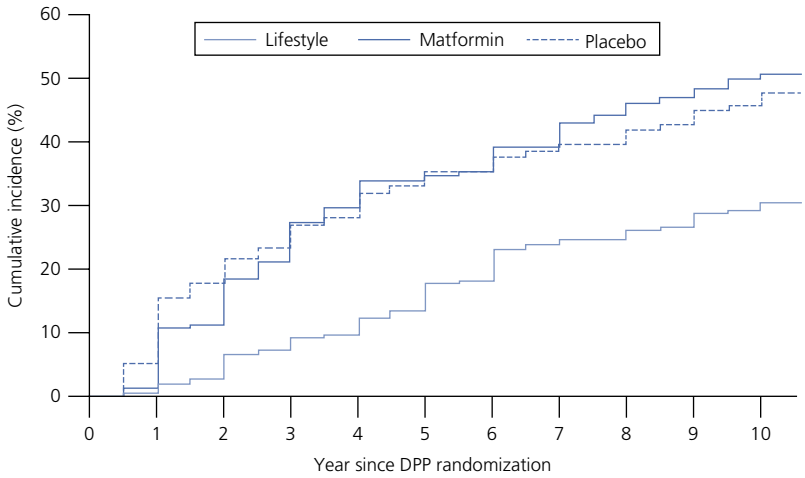

Figure 3.2 Cumulative incidence of diabetes over 10 years of follow-up in subjects age 60 years or older at randomization in the Diabetes Prevention Program Outcomes Study. Adapted from Diabetes Prevention Program Research Group. Lancet 2009; 374: 1677–86 with permission.

More recently, 10-year follow-up data from the DPP/DPPOS have been reported [30]. The key findings were that the ILS group gradually regained some of the weight lost during the active phase of the DPP, so that 4 years after randomization the mean weight loss was approximately 2 kg. It then remained at this level for the next 6 years. The initial weight loss observed in the metformin-treated group was approximately 3 kg and there was a slight increase over time so that after 10 years it has remained at approximately 2 kg below the baseline weight and approximately the same as that in the ILS group. The control subjects maintained their baseline weight or lost a slight amount after 9–10 years of follow-up. One striking finding was that the incidence rates for conversion to diabetes decreased significantly in the control and metformin groups, whereas they remained stable in the ILS groups. The respective diabetes incidence rates were 5.6 per 100 person years for the controls, 4.9 for the metformin group, and 5.9 for the ILS group. The reasons for this decrease in the incidence of diabetes in the control and metformin groups is not entirely clear, but may be due, in part, to exhaustion of the most susceptible participants and, in part, to the fact that both the control and metformin groups were given a 16-week course in the ILS program. Despite the decreased incidence rates for developing diabetes in the control and metformin groups, there is still a significant difference in the conversion rates among the three groups. Diabetes incidence in the 10 years since DPP randomization was reduced by 34% in the ILS group and by 18% in the metformin group, demonstrating that the effects of these interventions can persist for at least 10 years.

The long-term effects of the DPP interventions on CVD risk factors have also been evaluated [30]. After a median of 10 years of follow-up from randomization, significant reductions in blood pressure, LDL-C, and triglycerides, and increases in HDL-C were observed in all groups, with no significant differences among them. However, the ILS group had less use of medications to treat blood pressure or lipid abnormalities compared to their use in the control and metformin groups. In addition, the lifestyle program continued to be very effective in decreasing the progression to diabetes in older subjects, whereas treatment with metformin did not provide any benefit [26] (see Figure 3.2).

3.8 Translation of clinical trial results into clinical practice

The positive results of the major clinical trials such as the Da Qing study, the Finnish Diabetes Prevention study, and the DPP/DPPOS have led many groups to consider how to design and implement programs for lifestyle modification into clinical practice [37–42]. Such

programs may be based in practice offices, hospitals or the community. Economic analyses have concluded that conducting a program of lifestyle modification to reduce the incidence of diabetes is cost-effective [43] and many organizations have undertaken this task. These include various academic centers who are participants in the DPP/DPPOS who have developed programs for translation of the DPP/DPPOS results into clinical practice within their own institutions or in collaboration with community organizations, medical insurance groups or major employers. The Center for Disease Control (CDC) has also established a major initiative for diabetes prevention in the USA and is working closely with other organizations to implement their programs. Thus, there are now major efforts underway in the USA, as well as in other countries, to educate the population about the importance of eating a healthy diet, preventing or reducing obesity, and achieving adequate physical exercise with the goal of decreasing the incidence of diabetes and its long-term complications. Since lifestyle modification programs focusing on weight reduction, a healthy diet, and increased physical activity have been shown to be very effective in older people, it is generally agreed that this is the best approach to preventing diabetes in this high-risk population and should be adopted as a standard of care.

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CHAPTER 4
Diagnosis and screening

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KEY MESSAGES

- The diagnosis of diabetes mellitus should be made in the context of a comprehensive geriatric evaluation that includes a quantitative and qualitative assessment of different clinical, functional, preventive, and rehabilitative factors.
- There are two main objectives of any diagnostic or therapeutic procedure: improvement of life expectancy and optimization of health-related quality of life.
- All recent revisions (American Diabetes Association, World Health Organization) conclude that the diagnosis of diabetes should be based on classical symptoms and different blood glucose tests: random sample independent of prandial status, fasting glucose and 2-h plasma glucose after standardized metabolic stress test (oral glucose tolerance test), and HbA1c.
- In older people, the absence of symptoms or the presence of non-specific symptoms (fatigue, weight loss or behavioral changes) is the more usual clinical presentation of diabetes. Sensory alterations such as poor vision, decreased mobility, geriatric syndromes (cognitive impairment, falls), recurrent infections or painful syndromes are typical manifestations of diabetes mellitus in the oldest-old group.
- There is no satisfactory evidence to support screening in all those older than 75 years unless they have a high risk factor such as obesity, cardiovascular disease, hypertension or functional impairment.

4.1 Introduction

Until the 19th century, diabetes mellitus was considered to be a juvenile, rapidly evolving disease with a high short-term mortality rate. This clinical profile largely followed the prevalent pattern of infectious disease at that time when, for example, life expectancy in France in 1800 was less than 45 years (and it was one of the highest in the world). Two centuries later, in the 21st century, diabetes mellitus represents a chronic disorder of the middle-aged and the elderly with a low short-term mortality rate and a long-term stage of increased morbility, disability, and mortality. At present, average life expectancy of 45 years is the lowest in the world and can only be found in sub-Saharan Africa [1]. This different behavior of diabetes mellitus can be found particularly in developed countries thanks to progressive knowledge of diabetes mellitus resulting from the unyielding demographic and epidemiological transitional processes that occurred at that time. It was not until the last decades of the 20th century that developed countries began to explore the most efficient approach to the health, economic, and social consequences of the association between chronic disease and population aging. The relationship between diabetes mellitus and the elderly constitutes a clear example of this.

In 1980, two relevant contributions were made in the field of diabetes mellitus in the elderly: the compression of morbidity theory [2] and the WHO definition of the diagnostic criteria of diabetes mellitus [3]. Fries' hypothesis holds that if the age at the onset of the first chronic infirmity can be postponed more rapidly than the age of death, then the lifetime illness burden may be compressed into a shorter period of time nearer to the age of death.

Diabetes in Old Age, Fourth Edition. Edited by Alan J. Sinclair, Trisha Dunning, Leocadio Rodríguez Mañas, and Medha Munshi.

WHO provides the fundamentals to understand the role of diabetes mellitus in morbidity and disability in the aged population.

4.2 Definition of being old

An older person is defined as any individual aged 65 years or above. In developed countries, the population median values of chronic multimorbidity, disability, and mortality are close to 65, 75, and 85 years of age, respectively [4]. Accordingly, three age subsets can be found in the elderly population:

- The young-old group (65–74 years) encompasses a population with a high prevalence of chronic multimorbidity and a relatively low rate of frailty, disability, and mortality. Survival correlates, although not entirely, with the patients' functional level. This is the group where longitudinal studies are initiated in the elderly population.
- The middle-old/old-old group (75–84 years) has a high prevalence of multimorbidity, frailty, and disability. The atypical presentation of disease becomes "typical" with an increased frequency of geriatric syndromes and a functional impairment as the first symptom of disease. Survival is largely influenced by the patients' functional status.
- The oldest-old group (85 years and above) has a high morbidity, frailty, and disability rate. It is the population group where the incidence of disease selectively declines and the probability of death decelerates. The principle of "competitive mortality" [5] plays an important role in this population group. Survival is definitely influenced by the level of function.

The few medical publications addressing diabetes mellitus in the elderly, especially in the oldest group, advise us to read their conclusions with caution. In fact, the heterogeneity of the older population might suggest that research take into consideration the assorted subset of patients according to their location (hospital, community, nursing home), health/social resources requirements or quantity/quality of risk factors, morbidity, disability, frailty or mortality. The lifetime individual rate of biological aging might show great variability depending on several basic factors: the primary aging process, chronic disease (secondary ageing), acute disease, hormone-dependent modifications, habits/lifestyle, and the adaptive capacity of the individual. The summation of these factors yields a number of individual and specific characteristics that define a vital period: the senescence [6–8] (Figure 4.1).

The relevance, and consequently the risk–benefit ratio of the detection, diagnosis, prognosis, and treatment, of diabetes mellitus in the elderly is highly variable depending on the specific characteristics of each subject. A subject-based clinical approach is therefore mandatory.

4.3 Definition of diabetes

The concept of diabetes mellitus encompasses different processes of varying etiology and usually a progressive course that share a metabolic disorder (hydrocarbons, fat, and proteins), an altered endothelial and immune function, and an altered gene expression, all related to a deficiency in the secretion and/or action of the anabolic hormone by excellence: insulin. The basic biochemical characteristics of these processes derive from their catabolic action: greater blood availability of amino acids, free fatty acids, and glucose. Increased glucose blood levels (hyperglycemia) represent the most significant marker of diabetes mellitus. While the term "elderly" remains constant over time, the definition of diabetes mellitus relies on medical and scientific research, and hence it is largely dependent on the evolving diagnostic criteria.

4.3.1 Diagnosis

In older people, the diagnosis of diabetes mellitus should be made in the context of a comprehensive geriatric evaluation (CGE) that includes a quantitative and qualitative assessment of different clinical, functional, preventive, and rehabilitative factors [9].

- *Clinical factors*: Diet, blood pressure, intercurrent disorders, clinical or subclinical cardiovascular disease (CVD), pain, drug-taking history, and geriatric syndromes.
- *Functional factors*: Performance of basic, instrumental, and advanced activities of daily life, degree of self-care abilities, and measurement of different variables (cognitive status, frame of mind, gait, equilibrium, frailty [10], vision, hearing, and familial/social resources (living alone)).
- *Preventive factors*: Evaluation of habits and lifestyle, risk estimation (cancer, cardiovascular (high by

Figure 4.1 Principal features of the elderly: the cocktail of the senescence.

definition), infections, hypoglycemia (if previous diabetes mellitus)).

- *Rehabilitative factors*: Instructional programs to maximize physical, cognitive, and affective capabilities, and educational activities to enhance specific need-directed abilities.

The CGE provides the information required to design a coordinate long-term care plan. An exhaustive CGE should be done at least once every 3 years in the young-old group, every 2 years in the middle-old group, and annually in the oldest-old group. In the elderly diabetic, CGE should be done once every 2 years in the "young-old" group and yearly above 75 years of age [11].

4.4 Why investigate diabetes? Diagnostic objectives

4.4.1 Life expectancy and health-related quality of life

In older people there are two main objectives of any diagnostic or therapeutic procedure: improvement of life expectancy (LE) and optimization of health-related quality of life (HRQL) [12]. However, the presence of a vital limit [13] gives HRQL a growing importance as the elderly population gets older. Functional competence is the foundation of both LE and HRQL, and the most important predictive factor for disability, institutionalization, mortality, HRQL, and resource consumption in the elderly. Diabetes mellitus is a relevant risk factor in terms of both increased mortality rate and functional decline.

Statistical simulation models (Markov chain models) suggest that the diagnosis of diabetes mellitus in elderly women of 60, 70, and 80 years of age (with otherwise expected LEs of 26.5, 18.3, and 11.2 years, respectively) reduces LE to 17, 11.8, and 7.1 years, respectively. For males in the same age groups, with expected LEs of 22.2, 14.9, and 9.4 years, respectively, real LE drops to 14.9, 9.6, and 5.6 years, respectively, in the presence of diabetes mellitus [14]. However, these data have not been confirmed by other observational studies. A UK study by Tan *et al.* [15] did not find differences in mortality between recently diagnosed diabetes mellitus elderly patients and the general non-diabetic population whereas in elderly women a difference in mortality was found 3 years after the diagnosis.

Diabetes can have a negative impact in every functional domain: physical [16], cognitive [17], affective [18], sensorial [19], and social [20]. This functional decline is partly explained by specific microvascular (eye, kidney, and peripheral nerves) or non-specific cardiovascular (coronary, cerebrovascular or peripheral arterial) complications of diabetes mellitus but near 60% excess prevalence of disability remains after adequate control of these factors [21]. With a greater impact on function than LE, the diagnosis of diabetes mellitus is paramount in the therapeutic approach in the elderly.

4.4.2 Diagnosed and undiagnosed diabetes mellitus

Two groups are found in older patients with a clinical diagnosis of diabetes mellitus: senile diabetes [22] (or elderly onset diabetes mellitus) and middle-age onset diabetes mellitus; both are unfortunate, politically incorrect terms! A US transverse study by Selvin *et al.* [23] indicates that elderly onset diabetes mellitus is only responsible for 15% of the diabetes mellitus diagnosis in the population aged 20 years or over. This 15% of elderly onset diabetes mellitus represents 40% of the elderly diabetes mellitus population overall, the remaining 60% corresponding to the middle-age onset diabetes mellitus group.

The proportion of undiagnosed to diagnosed diabetes mellitus increases with age, the proportion of undiagnosed being around 45% in the elderly (young-old 42.6%, middle-oldest plus old 46%) [24]. In Spain, the rates of diabetes mellitus in young-old and middle-oldest groups are 41.5% and 44.6%, respectively, in men and 37.2% and 43.8% in women [25]. Accordingly, the diagnostic effort in the elderly should be directed towards the recognition of new and undetected cases.

4.5 How to recognize diabetes mellitus: Diagnostic tools

Historically, all diagnostic criteria of diabetes mellitus included two key elements: symptomatology and glucose levels in urine or blood. Until the first quarter of the 20th century, classical symptoms of diabetes mellitus (polyuria, polydipsia, polyfagia, unintentional weight loss) and the presence of reducing substances in the urine were the hallmarks of diagnosis. In 1919, Folin and Wu [26] introduced the determination of blood glucose. Only 2 years later, Banting and Best discovered insulin. Because of the recognition of specific long-term microvascular complications, the diagnosis of asymptomatic diabetes mellitus (mainly type 2) through the detection of high blood glucose levels has become paramount in clinical practice, a fact that has allowed physicians to minimize diabetes mellitus complications more than treat the disease itself.

4.5.1 Symptomatology

In the elderly, the absence of symptoms or the presence of non-specific symptoms (fatigue, weight loss or behavioral changes) is the more usual clinical presentation. Classical pre-acute symptoms (polyuria, polydipsia) are less sensitive because the kidney threshold to remove blood glucose is higher in the elderly than in the adult patient. Weight loss and urine ketone are less specific because they are can be found in numerous catabolic disorders. Sensory alterations such as poor vision, decreased mobility, geriatric syndromes (cognitive impairment, falls), recurrent infections or painful syndromes are typical manifestations of diabetes mellitus in the oldest-old group [11].

4.5.2 Blood glucose tests

The measurement of blood glucose can be done as a basal or static test, under fasting conditions, or a dynamic test after oral intake of a glucose overload that recreates the homeostatic reserve of the individual. The sequential combination of both measurements represent the oral glucose tolerance test (OGTT) [27].

4.5.2.1 The oral glucose tolerance test

The OGTT is a medical test in which glucose is given and blood samples taken afterwards to determine how quickly it is cleared from the blood. It was first described as a research tool in the 1920s [28] and was paramount in the diagnosis of diabetes mellitus for decades. The OGTT was initially recognized as a diagnostic tool in Fajans-Conn's criteria [29] in 1959 and the WHO finally validated it in 1965 [30] (subsequently confirmed in 1980 [2], 1985 [31], 1999 [32], and 2006 [33]). The OGTT evaluates the physical efficiency to metabolize glucose and has been considered the "gold standard" test in the diagnosis of diabetes mellitus for decades.

The OGTT should be administered in the morning (7.00–9.00am) after at least 3 days of unrestricted diet (greater than 150 g of carbohydrate daily), normal

physical activity, and in the absence of any drug that might significantly alter the carbohydrate metabolism. The patient is instructed to fast (water is allowed) for 8–12 h prior to the test. Smoking is not permitted during the test and the presence of factors that influence interpretation (medications, infection, etc.) must be recorded [32]. At present, the test consists of the extraction of a blood sample from a vein in the arm for the measurement of fasting plasma glucose (FPG), the administration of 75 g of anhydrous glucose (or its equivalent) in a final volume of 300 ml of water, and a new blood extraction for the measurement of plasma glucose 2 hours later (2h-PG). The most widely accepted glucose-based criteria for diagnosis of diabetes mellitus are FPG > 126 mg/dl (>7 mmol/l) or a 2h-PG > 200 mg/dl (> 11.1 mmol/l) [33].

4.5.2.2 Fasting plasma glucose

Basically, FPG represents the level of basal pancreatic insulin secretion and its action over the liver cells. Consequently, an increased FPG determines a reduced insulin secretion in absolute terms associated with a greater or smaller resistance of liver cells to insulin [34, 35]. The measurement of FPG has the advantage of its high availability, being an inexpensive assay on automated instruments that is available in most laboratories worldwide. However, the disadvantage of the measurement includes an overnight fast for at least 8 hours, the influence of acute illness or stress, high inter-laboratories variability, and high intra-individual biological variation, with a reported coefficient of variability (CV) ranging from 5.7% to 8.3%. Based on a CV of 5.7%, FPG can range from 112 to 140 mg/dl (confidence interval of 95%) in a subject with an FPG of 126 mg/dl [36].

4.5.2.3 Two-hour plasma glucose

2h-PG levels represent the ability of the β-cells of the pancreas to increase the basal secretion of insulin and show the capacity of action of insulin over the peripheral tissues, mainly muscle and fat. An increased 2h-PG thus represents a relative deficit of insulin due to an increased resistance of myocytes and adipocytes to insulin [34, 35].

An increase in postprandial glucose concentration usually occurs before fasting glucose increases. This condition, known as isolated post-challenge hyperglycemia (IPH) [37], is defined by FPG < 126 mg/dl (<7 mmol/l) and 2h-PG > 200 mg/dl (>11.1 mmol/l) and is more common in the elderly than in the younger adult. The risk of cardiovascular long-term morbidity and mortality associated with IPH is very similar to the risk found in the elderly diabetic group with a recent diagnosis of diabetes mellitus. For that reason, IPH is now included in the diagnostic criteria of diabetes mellitus (2h-PG > 200 mg/dl (>11.1 mmol/l).

The reasons for the benefit of OGTT in the elderly, and consequently the measurement of 2h-PG against FPG alone, are two-fold: the detection of an important number of elderly diabetics included in the impaired fasting glucose (IFG) group and the detection of elderly diabetics (or those included in the impaired glucose tolerance (IGT) group) in the normoglycemic group. The IGT group has an increased risk of diabetes mellitus and CVD when compared with the general population with normal glucose levels [38, 39].

The main disadvantage of OGTT versus FPG in the elderly is the much lower availability because of the extensive requirements of patient preparation and lower patient tolerance to undergo the test. Additional limitations include a higher intra-individual variability (CV 15–18.3%) [40] and a higher cost when compared with FPG. All these factors led the American Diabetes Association (ADA) to conclude in 1997 that FPG should be the recommended glucose-based test [41].

4.5.2.4 HbA1c

Measurements of glycated proteins, mainly hemoglobin (Hb), can quantify the average glycemia over an extended period of time, thus enhancing the information of FPG measurements. Adult human hemoglobin is heterogeneous, HbA involving nearly 90% of the total hemoglobin. The term HbA1c is used to describe a specific and stable minor HbA component generated slowly and non-enzymatically from HbA and glucose. The production rate of HbA1c is directly proportional to the ambient glucose concentration. Because erythrocytes are freely permeable to glucose, the level of HbA1c in a blood sample represents the glucose levels of the previous 120 days, the average erythrocytes lifespan [42]. HbA1c reflects the chronic exposure to basal and postprandial hyperglycemia and could be the result of different risk phenotypes. The conversion formulae from HbA1c to average plasmatic glucose (APG) in subjects 18–70 years old is as follows: APG (mg/dl) = (28.7 × HbA1c(%)) – 46.7 and APG (mmol/l) = (1.59 × HbA1c(%)) – 46.7 [43]. HbA1c was introduced into

clinical practice in the 1980s and is at present an important parameter in the management of diabetes mellitus because of its triple condition of diagnostic method, prognostic marker, and therapeutic objective. Paradoxically, the inclusion of HbA1c as a diagnostic tool has only recently been made. The unit of measurement of HbA1c recommended by the International Federation of Clinical Chemistry (IFCC) is mmol/mol [44].

The main advantages of HbA1C include that it can be performed any time of day, does not require fasting, is not affected by acute illness, short-term lifestyle or drugs changes, and has a low CV (ranging from 32% to 4%). Its main shortcomings include the need for standardization in developing countries, a higher economical cost, variations arising from ethnic race, and the presence of different factors that can alter the average expected life of the erythrocyte. Different factors have been found to increase HbA1c in the elderly: iron deficiency anemia, vitamin B_{12} deficiency anemia, myelodysplastic syndromes, chronic renal insufficiency, and the long-term use of opioids. Factors involved in the diminution of HbA1c include hemoglobinopathies, liver cirrhosis, splenomegaly, hemolytic anemia, hypertriglyceridemia, hyperbilirubinemia, and recent blood transfusions [45, 46].

4.6 Diagnostic criteria

4.6.1 Glucose level for diagnosis of diabetes mellitus

The level of blood glucose is a continuous variable and any cut-off value to discriminate pathological from physiological glucose concentrations is probably arbitrary. Type 1 diabetes mellitus has a characteristic clinical and biochemical profile, and specific blood glucose threshold values are not required in most clinical cases. On the contrary, type 2 diabetes, representing 90% of diabetes mellitus in the elderly [47], has a more treacherous onset and is characterized by a slow increase in glucose levels over time. The question of which value of hyperglycemia should be diagnostic of type 2 diabetes mellitus has been long debated. The first 1965 WHO criteria [30] were based on a statistical abnormality (the mean plus two standard deviations of glucose levels after an oral glucose load in non-older healthy subjects), but that statistical abnormality does not necessarily correlate with a clinical abnormality.

Because of the poorly defined existing criteria of diabetes mellitus [48], the National Diabetes Data Group (NDDG) [49] undertook in 1979 an in-depth consensus to define the worldwide diagnostic criteria of diabetes mellitus. These new standards were incorporated by WHO in 1980 [2]. In non-elderly adult populations (Pima Indians, Micronesians) with a high prevalence of diabetes mellitus (more than 15%), the plasma glucose levels express a bimodal distribution both in fasting (FPG) and stress conditions (2h-PG). This distribution is defined by the consecutive appearance of two Gaussian curves as the glucose levels increase. The intersection point of minimal overlapping between these two Gaussian curves defines the cut-off that determines the diagnosis of diabetes mellitus. Its value is 140 mg/dl for FPG and 200 mg/dl for 2h-PG. At the same time, the long-term longitudinal cohort studies of the Pima Indians [50] in the USA (3–8 years), Whitehall [51] (5 years), and Bedford [52] (10 years), both in the UK, all with an extremely low elderly population, indicate that these threshold values are predictive of an increased risk of retinopathy. Subsequently, in 1997, the ADA lowered the FPG value in the diagnosis of diabetes mellitus to 126 mg/dl after a revaluation of the transverse relationship between FPG and retinopathy [41]. Furthermore, the revision permitted an increase in diagnostic sensitivity and the consistency between FPG and 2h-PG (200 mg/dl) values. Thereafter, both WHO and ADA have made new revisions.

4.6.2 Current diagnostic criteria

The most recent ADA review was published in 2014 [53] while WHO released updates in 2006 [33] and 2011 [46] (Table 4.1). All these revisions conclude that the diagnosis of diabetes mellitus should be based on classical symptoms and different blood glucose tests: random sample independent of prandial status, fasting glucose, and 2h-PG after standardized metabolic stress test (OGTT) and HbA1c. The use of HbA1c was incorporated by ADA [54] in 2010 and by WHO [46] in 2011.

At present, ADA recommends the use of both FPG and HbA1c in the diagnosis of diabetes mellitus. WHO recommends 2h-PG and FPG, although HbA1c might also be used. The current cut-offs for the diagnosis of diabetes mellitus are ≥126 mg/dl (>7 mmol/l) for FPG, ≥200 mg/dl (≥11.1 mmol/l) for 2h-PG and ≥6.5% (≥48 mmol/mol) for HbA1c.

Table 4.1 Diagnostic criteria of glucose metabolism abnormalities.

Category	ADA-2014	OMS-2006/2011/IDF-2013*	EDWPOP-2011
Diabetes	FPG > 126 mg/dl (>7 mmol/l) or 2h-PG > 200 mg/dl (>11.1 mmol/l) or HbA1c > 6.5% (> 48 mmol/mol)	(*IDF-2013 only for diabetes diagnosis) FPG > 126 mg/dl (>7 mmol/l) or 2h-PG > 200 mg/dl (>11.1 mmol/l) or HbA1c > 6.5% (>48 mmol/mol)	FPG ≥ 126 mg/dl (≥7 mmol/l) or 2h-PG ≥ 200 mg/dl (≥11.1 mmol/l)
Diabetes	Hyperglycemia symptoms or hyperglycemia crisis and random PG > 200 mg/dl (>11.1 mmol/l)		
Pre-diabetes/IH IFG	Pre-diabetes FPG > 100 mg/dl (>5.6 mmol/l) and < 126 mg/dl (<7 mmol/l)	Intermediate hyperglycemia FPG > 110 mg/dl (>6.1 mmol/l) and < 126 mg/dl (<7 mmol/l) (and if measured) 2h-PG < 140 mg/dl (<7.8 mmol/l)	Pre-diabetes FPG > 110 mg/dl (>6.1 mmol/l) and < 126 mg/dl (<7 mmol/l) and 2h-PG < 140 mg/dl (<7.8 mmol/l)
Pre-diabetes/IH IGT	Pre-diabetes FPG < 126 mg/dl (<7 mmol/l) and 2h-PG > 140 mg/dl (> 7.8 mmol/l) and < 200 mg/dl (<11.1 mmol/l)	Intermediate hyperglycemia FPG < 126 mg/dl (<7 mmol/l) and 2h-PG > 140 mg/dl (>7.8 mmol/l) and < 200 mg/dl (<11.1 mmol/l)	Pre-diabetes FPG < 126 mg/dl (<7 mmol/l) and 2h-PG > 140 mg/dl (>7.8mmol/l) and < 200 mg/dl (<11.1 mmol/l)
Pre-diabetes	Pre-diabetes HbA1c > 5.7% (>39 mmol/mol) and < 6.5% (<48 mmol/mol)	No	No
Norm glycaemia	FPG < 100 mg/dl (<5.6 mmol/l) or 2h-PG < 140 mg/dl (<7.8 mmol/l) or HbA1c < 5.7% (<39 mmol/mol)	FPG < 110 mg/dl (<6.1 mmol/l) or 2h-PG < 140 mg/dl (<7.8 mmol/l)	FPG < 100 mg/dl (<5.6 mmol/l) or 2h-PG < 140 mg/dl (<7.8 mmol/l)

FPG, fasting plasma glucose; 2h-PG, 2-hourly plasma glucose; HbA1c, hemoglobin HbA1c; IH, intermediate hyperglycemia; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Two specific guidelines provide diagnostic criteria for diabetes mellitus in the elderly: the 2004 European Diabetes Working Party for Older People (EDWPOP) [11] and the 2013 International Diabetes Federation (IDF) (older people with type 2 diabetes) [55]. In the first case, these criteria arose from the WHO consultation (1998) and the 1997 and 2004 ADA Expert Committee criteria. Later, the 2011 EDWPOP [56] clinical guideline for type 2 diabetes mellitus reinforced the concept that diagnosis of diabetes mellitus in the elderly should be in accordance with published national/international criteria and that no age-modified criteria could be recognized. In the second case, IDF criteria came from 2006–2011 WHO guidelines.

Unlike epidemiological studies, which only require one measurement, the clinical diagnosis of diabetes mellitus requires a second measurement by the same diagnostic method or the coincidence of two abnormal tests in the first measurement (FPG and HbA1c). Usually, a second measurement involves a diminished prevalence of diabetes mellitus by 30% for FPG and 16% for HbA1c [40].

4.6.3 Aging and glucose tolerance

The association between the reduction of glucose tolerance and the aging process, in patients older than 60 years, was first reported by Spence in 1920 [57]. This finding, confirmed by other transverse and longitudinal studies [58, 59], is more relevant in stress dynamic (2h-PG) than in baseline (FPG) conditions. From the age of 30, the mean value of increase per decade in plasma glucose levels is 0.8–1 mg/dl for FPG, 5 mg/dl for 2h-PG, and 0.1% for HbA1c [60]. As a consequence, between a 30-year adult and an 80-year elderly person, age by itself might explain a difference of 5 mg/dl in FPG, 25 mg/dl in 2h-PG, and 0.5% in HbA1c. Accordingly, the diagnostic threshold of diabetes mellitus might need to be raised to 131 mg/dl (FPG), 225 mg/dl (2h-PG), and 7% (HbA1c) for the middle-old and oldest-old groups, something that has not been contemplated by any of the present diagnostic standards.

4.6.4 Test consistency: FPG, 2h-PG, and HbA1c

The cut-off diagnostic values of diabetes mellitus increase the risk of retinopathy, CVD, and mortality. The DETECT-2 project [61], an international data-pooling collaboration program in the adult population, validates the association of FPG, 2h-PG, and HbA1c with an increased prevalence of retinopathy. In the elderly, the Cardiovascular Health Study (CHS) [39] has reported that a recent diagnosis of diabetes mellitus, determined by FPG or 2h-PG, is associated with an increased relative risk of CVD (1.58 and 1.56, respectively). The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study group [62] has confirmed that a recent diagnosis of diabetes mellitus defined by 2h-PG, more than FPG, is consistently associated with an overall increased relative risk of death (2.02 vs 1.81 in men and 2.77 vs 1.79 in women, respectively). Finally, the Atherosclerosis Risk in Communities (ARIC) study [63], a prospective epidemiologic study conducted by the US National Heart, Lung, and Blood Institute, has reported that HbA1c is more strongly associated with CVD and overall mortality than FPG. However, no research has been done to elucidate the eventual relationship between FPG, 2h-PG or HbA1c and functional disability. In summary, the above-mentioned studies conclude that HbA1c, and to a lesser extent 2h-PG and FPG, is particularly associated with an increased risk of retinopathy, CVD, and death.

4.6.4.1 FPG and 2h-PG

In the older US population, data from CHS reveal that the prevalence of undiagnosed diabetes mellitus defined by 2h-PG is double that of FPG-defined cases (14.8% vs 7.7%) [64]. Of the detected cases by FPG, 81.9% could be diagnosed by 2h-PG. Of the detected cases by 2h-PG, only 42.9% could be diagnosed by FPG.

In an elderly European population data from the DECODE study group [65] show similar conclusions. In the age range from 70 to 79, the prevalence of undiagnosed diabetes mellitus by 2h-PG and FPG is 8.9% and 5.7%, respectively. In females, 59.6% of undiagnosed diabetes mellitus by FPG could be detected by 2h-PG. However, only 38% of females with undiagnosed diabetes mellitus by 2h-PG could be detected by FPG. Overall, in undiagnosed diabetes mellitus by both tests (100% = 11.7%), nearly 25% (2.8%) included FPG and 2h-PG, 50% (6.1%) included only 2h-PG and 25% (2.9%) included only FPG. These data suggest that 2h-PG is a better test than FPG in the diagnosis of diabetes mellitus in the elderly.

4.6.4.2 FPG and HbA1c

A recent research done in the elderly cohort of the Health ABC Study [66] ($n = 3075$, 48.4% male, 41.6% black, aged 70–79) reveals that, of 1865 participants without a history of diabetes, 1785 (95.7%) had both HbA1c below 6.5% and FPG below 126 mg/dl. Of those found to be diabetic by either FPG or HbA1c ($n = 80$) roughly equal numbers were identified solely by one method or simultaneously by both: 27.5% ($n = 22$) only by FPG, 36.3% ($n = 29$) only by HbA1c, and 36.3% ($n = 29$) by both methods. This finding suggests that both tests are supplementary in the diagnosis of diabetes mellitus in the elderly.

4.7 Diagnostic approach

The diagnostic protocol of diabetes mellitus relies on several factors, including risk associations, intrinsic characteristics, economic cost, and test availability. Central features of the test should be its simplicity and convenience for both patients and physicians, something that is highly dependent on sociocultural and economic environment of the target population. Figure 4.2 illustrates a practical clinical approach in the diagnosis of diabetes mellitus in the European elderly community.

4.8 Screening

The ideal conditions for a screening policy compel us to answer the following questions regarding the illness [67]:

1. Does it involve a public health issue? Over 25% of people older than 75 are affected by this sickness. It facilitates the emergence of disabling, chronic diseases, increases hospital admissions and their duration, causes physical and psychological disabilities, and involves a substantial consumption of social and sanitary resources.
2. Does it have a long pre-clinic period? Its patho-chronology is not well known, but it is considered to have a long pre-clinic period due to its scarce symptomatology, as the prevalence of the non-diagnosed

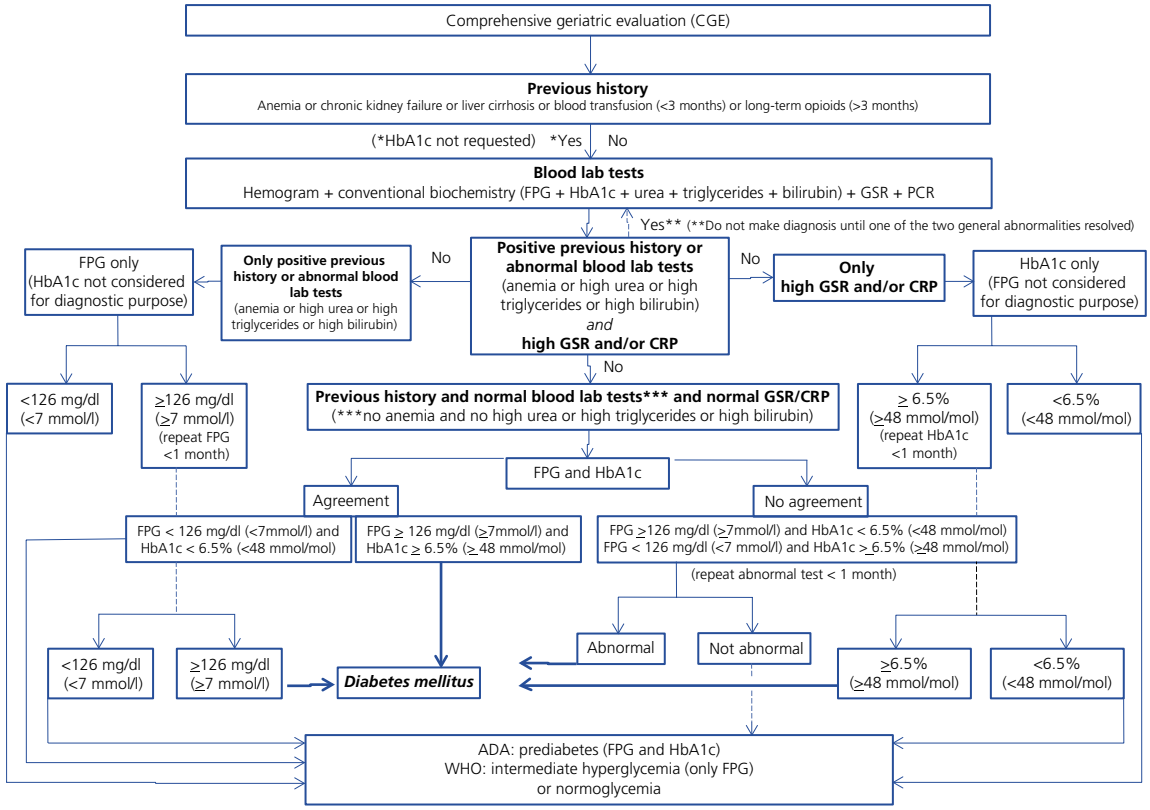

Figure 4.2 Practical clinical approach in the diagnosis of diabetes mellitus in the elderly. HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; GSR, globular sedimentation rate; CRP, C-reactive protein; ADA, American Diabetes Association; WHO, World Health Organization.

illness oscillates between 25% and 40% of patients older than 75 years [25].

3 Do we have reliable diagnostic tools? The diagnostic tools are easy and reliable.

4 Does early treatment imply a better prognosis? We do not possess enough evidence, nevertheless expert geriatricians advise treatment to reduce acute complications, opportunistic infections, improvement of cognitive decline, and reduction of physical impairment. In this sense, the conclusions of the MidFrail Study, currently developing in Europe, will resolve this issue. A study performed in the UK increases the complexity of this decision. The authors arranged three groups: two of them underwent a screening in which those who were positive could be subjected to a strict control or just the usual controls, and a third group did not undergo any screening. After 9.6 years of follow-up, with an average age of 59 years old, there were no significant differences regarding cardiovascular, cancer or global mortality [68].

5 Is it cost-effective? We have no solid evidence but there are studies based on computerized mathematic models that suggest that, in the elderly, it is cost-effective, although not as much as in the 30–45-year-old group.

6 Can the screening cause harmful effects? The anxiety caused by false positives seems exceptional, but the infradiagnosis can lead to an abandonment of healthy habits, such as exercising, quitting smoking, following a healthy diet or managing weight. To the threat of the huge prevalence of non-diagnosed illness, it adds the fear of the enormous predicted growth all around the world, especially in developing countries. According to the IDF there are 382 million diabetics aged under 80 years old and by 2035 the number will have increased to 592 million patients diagnosed [69].

A 2001 study, published in the USA, found a prevalence of 14% in patients older than 75 years, with a foreseen growth of 22% by the year 2050, that is, an increase of more than 50% [70]. This epidemic will affect mainly the elderly population living in developing countries, so in 2025 75% of diabetic patients will live in those countries, mainly in urban areas [71].

The high prevalence of undiagnosed diabetes mellitus is considered by some institutions, such as the IDF and the ADA [53], to suggest a policy for screening of diabetes mellitus in people over 75 years old. Other institutions, such as the United States Preventive Service Task Force (USPSTF) [72], recommend a different attitude, for example it does not take into account the age of a subject, and concludes that in the absence of hypertension there is no evidence that screening for diabetes mellitus is suitable. A third position is the National Institute of Clinical Excellence (NICE) attitude. NICE recommends screening of people at high risk who are 75 years old or older. The risk is defined using a self-questionnaire that includes hypertension, obesity, age, and familial history [73]. The population classified as low or intermediate risk should be advised to follow a healthy lifestyle and informed of the advantages of modifying risk factors.

This policy is based on grade C recommendations therefore it is very important for the clinicians who focus on this problem to make decisions on an individual basis, knowing the risk factors for developing diabetes mellitus in each patient. Risk-assessment tools are available to help in these decisions, for example CANRISK, FINRISK, AUSDRISK, and Qdiabetes risk scores, but most of them have not been validated in elderly people. They include information about sex, age, blood pressure, sedentary behavior, and BMI. More complex traits did not improve the predictive value of the assessment [74].

We should improve our knowledge of the following risk factors:

- *Ethnicity*: The risk for developing diabetes mellitus is increased for Asians, Hispanics and African Americans. Today some international institutions estimate that there are 382 million diabetic people all around the world, 210 million of whom live in southern Asia and the western Pacific countries. China and India are included in this increase [75, 76].
- *Abnormal glucose metabolism* (IGT and IFG): Both disturbances increase the risk for developing diabetes mellitus although they are physiopathologically different because the first is dependent on muscle resistance to insulin while the other is a problem of insulin liver resistance. They raise the risk of developing diabetes mellitus by 10–20-fold, with an incidence of 36–87 per 1000 person-years, regardless of age. It is interesting that the preventive power of lifestyle changes is such that risk can be reduced by 58% over 4 years [77].
- *Obesity*: The risk of diabetes mellitus associated with high BMI is greater in people under 75 years old but persists over this age. Obesity can increase diabetes mellitus prevalence by 50% in men and 100% in women [78]. We do not know exactly the role of fat distribution in older people, but it seems that the presence of central obesity is not as powerful as it is in younger adults, and the role of fat muscle infiltration is also unknown [79].
- *Exercise*: The benefit of exercise in the prevention of diabetes mellitus is clear, especially in high-risk populations. Doing more than 150 minutes of moderate intensity exercise weekly is enough to reduce the risk of diabetes mellitus. Those at high risk, especially patients with abnormal glucose metabolism (AGM) should be the target population [80].
- *Hypertension*: It seems that hypertension, after AGM and obesity, is the most powerful risk factor for developing diabetes mellitus and may be related to insulin resistance. It is therefore noteworthy that USRCTF considered hypertension to be the only factor to take into account in a screening policy.
- *Cardiovascular diseases*: Acute coronary syndromes and heart failure appear to be associated with a significant risk of diabetes mellitus after controlling for other diabetes mellitus risk factors.
- *Hyperuricemia*: This is not as important as other risk factors but contributes to the development of diabetes mellitus and may be mediated by insulin resistance or oxidative stress.
- *Others lifestyle habits*: These include diet, alcohol consumption, smoking cigarettes, and sleeping pattern. There are some studies, not specifically designed for older people, that conclude that sleeping less than 6 h per day is associated with an increased risk of diabetes mellitus compared to those who sleep more than 8 h per day [81]. This effect is attenuated but persists after adjusting for BMI. This effect may be related to melatonin secretion, a independently associated feature of the risk of developing diabetes mellitus [82].

Some studies have raised the possibility of smoking being associated with increased risk of diabetes mellitus, and it appears to be graded as the pack-year history rises [83]. Diabetes mellitus risk is reduced by decreasing the number of smoked cigarettes. Diet is also very important. A significant increase in diabetes mellitus is seen in those who eat a western diet, composed of high red meat, processed meat, and sugar sweetened beverages intake, and low fruit and greens intake. After adjusting for other variables such as BMI, age, familial history of diabetes mellitus or physical activity, this population has a relative risk of 1.

- If the population with this diet are obese the relative risk increases to 11 [84]. On the other hand, a Mediterranean diet, characterized by high intake of fruit, vegetables, olive oil, whole grain, nuts and fish, reduces the relative risk, but this study was conducted in younger adults [85].
- *Functional impairment:* Functional decline is one of the most important complications of diabetes mellitus. The physiopathology is not well understood in at least 50% of cases because well-known chronic complications do not explain it. It seems that reciprocal correlation may be seen because some studies show that diabetes mellitus is more prevalent in functional impaired elderly patients. We do not know the relationship but diabetes mellitus is more prevalent in frail and pre-frail patients than in the general population. This issue is one of the leading points of geriatric assessment but there isn't a risk score to predict diabetes mellitus that includes functional assessment. Cognitive impairment is also not included. Screening in older patients should be always completed with some degree of functional assessment.
- *Screening in nursing homes:* The prevalence of diabetes mellitus is greater in nursing home patients than in elderly people in the community, with 27–30% in UK [86] and 35% in the US [87]. The prevalence of undiagnosed disease is unknown, but risk factors are more frequent. Diabetic patients in nursing homes have an increased risk of hospital admission and longer stay, more co-morbidity, and take more drugs than diabetic patients living in the community. The typical diabetic patient admitted to a nursing home is a woman, 75–84 years old, discharged from hospital, with low income, scant social support, high cardiovascular comorbidity, 69% with hypertension, 35% with ischemic heart disease, 26% with heart failure, 23% with history of stroke, and 14% with peripheral vascular disease, with some degree of cognitive impairment in 50% [88, 89]. Thus some experts think that screening should be routinely undertaken in nursing home residents because they are a very high risk population for diabetes mellitus.

In conclusion, we have no satisfactory evidence to support screening in all those over the age of 75 unless they are at high risk. Some guidelines recommend screening for individuals of all ages, but this is a grade C recommendation. Probably a better option is to offer screening to those at high risk (with at least one risk factor, e.g. hypertension, obesity, CVD, functional or cognitive impairment, AGM [90]). The rest of the population should be advised about the benefits of a healthy lifestyle and how to modify risk factors.

Diabetes mellitus is a public health problem mainly in the aged population. Given its high prevalence and consequences we should implement relevant knowledge about the disease, its pathophysiology, risk factors, and preventive measures to establish an effective screening policy and promote responsibility in the target population for their own health management.

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CHAPTER 5

Assessment procedures including comprehensive geriatric assessment

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KEY MESSAGES

- A *patient-centered approach* that considers the full complexity of the disease (i.e., hypoglycemic risk, diabetes duration, and vascular complications) and incorporates additional clinical factors (other co-morbidities, functionality, psychological, and socioeconomic factors) is now seen as a standard of care.
- It is important to highlight the relevance of screening for geriatric syndromes through a tailored comprehensive geriatric assessment (CGA) and patient-centered management of diabetes in older people.
- A CGA increases a patient's likelihood of being alive and in their own homes after an emergency admission to hospital.
- CGAs can take different forms according to the global health status of the older patient and according to the living situation: home living, hospitalization or admittance to hospital.
- Other aspects of the disease, including pathophysiology, diagnostic criteria, dosing and side effects of medications, dietary consideration, exercise strategies, and impact of the disease on quality of life, also require special considerations.

5.1 Diabetes in the aging population

The aging population is growing around the world. There will be 2 billion people older than 60 by 2050 [1]. Using data from the International Diabetes Federation (IDF) atlas, it is estimated that the proportion of older adults among those with diabetes could reach 41% by the year 2030 (i.e., increasing from nearly 135 million in 2013 to more than 226 million in 2030), which represents a major health and financial burden. Older adults are at higher risk of type 2 diabetes due to the combined effects of increasing insulin resistance and impaired pancreatic islet function with aging. They may either have incident disease or long-standing diabetes with onset in middle age or earlier, with varying clinical characteristics and implications for individualized interventions [2]. While less frequent, the aging population will also present with incident type 1 diabetes, with a growing prevalence of long-standing cases.

Diabetes is a complex chronic disease, with multiple complications and associated co-morbidities, which by itself may accelerate the aging process. Both tissue accumulation of advanced glycation end products and the high incidence of atherosclerotic disease have been proposed as contributing factors to aging. Additionally, with increasing age and duration of disease, both micro- and macrovascular complications are more prevalent in the elderly [3]. Diabetes and obesity are known risk factors for the development of physical disability among older adults. Their interaction may further accelerate sarcopenia and place obese older adults with diabetes at particularly high risk of disability [4].

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The needs of older people with chronic diseases are complex, with potentially coexistent medical, functional, psychological, and social needs [5]. In clinical practice, diabetes management in older people is not as straightforward as it can be in younger individuals, who usually present with fewer co-morbidities and without emotional, cognitive or physical function limitations. Moreover, applying a disease-centered approach may result in glycemic targets and treatment that appear effective on the surface but inappropriate, unrealistic, and unsuccessful in older patients. In contrast, a *patient-centered approach* that considers the full complexity of the disease (i.e., hypoglycemic risk, diabetes duration, and vascular complications) and incorporates additional clinical factors (other co-morbidities, functionality, psychological, and socioeconomic factors) [6] has been proposed as a standard of care, even though the outcomes from patient-centered interventions on micro- and macrovascular complications are still unknown.

There is heterogeneity among older adults with diabetes. Some of them have limitations in the functional, psychological, and social domains, leading to greater disease burden, affecting targets and priorities, increasing their risk for hypoglycemia, and limiting access to medications [7]. Geriatrics syndromes are more common in older adults with diabetes therefore their clinical management must incorporate *comprehensive geriatric assessment* (CGA) in the already well-established comprehensive diabetes evaluation (CDE) [8]. This may lead to better glycemic control and prevent further functional decline in older adults with diabetes [9]. This chapter explores the geriatrics approach to diabetes in older people, highlighting the relevance of screening for geriatric syndromes through a tailored CGA and patient-centered management of diabetes in older people.

5.2 Geriatric syndromes in an aging population

As we age we are at greater risk of developing functional and cognitive decline, chronic medical diseases, and *geriatric syndromes*, such as polypharmacy, cognitive impairment, urinary incontinence, injurious falls, frailty, persistent pain, impaired mobility, and depression, which will add further complexity to the management of diabetes in older people [1, 10, 11]. These syndromes may lead to poor quality of life and even loss of independence, requiring transition to assisted-living facilities, community-living centers or nursing homes. Geriatric syndromes are multifactorial, but shared risk factors and pathophysiologic mechanisms raise the possibility of a unified approach for the prevention of these syndromes. However, screening for and detection of the presence of geriatric syndromes is a key factor for management, even if the final diagnosis is not ultimately found [12].

A few medical specialties have described the need to address the geriatric domains to provide individualized care for older patients [13]. Some have incorporated a CGA in frail older patients and showed improvement in the medical care of patients with cancer [14]. There are varying definitions proposed for frailty [15], and the CGA provides a framework to assess the impact of frailty in patients with diabetes and take into account the availability of the resources needed in the healthcare system.

5.3 CGA and the geriatrics approach to diabetes

A CGA can be indicated for any complex patient whose conditions or diseases impact more than just the medical domain (Tables 5.1–5.4). Furthermore, the assessments cannot be limited to the disease alone, but to the person as an individual. This is important in providing an individualized approach, selecting glucose targets and pharmacologic interventions, and assessing the feasibility of implementation in clinical practice. The assessment of the four geriatrics domains is extremely important in the selection and monitoring of pharmacologic interventions for diabetes [16].

The CGA was developed in the 1930s by British geriatricians. For several decades it offered a multidisciplinary model of care for high-risk older adults, within the hospital setting [17], and it was then implemented in the outpatient setting, where it is not restricted to the geriatrics specialty [18]. The CGA has been defined as multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological, and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up [19]. The procedure enables the measurement and analysis of a complex situation (that of the frail elderly person) by converting qualitative elements into quantitative elements (scores), and contributes to the development of a comprehensive care plan [20].

When followed up by targeted action, the CGA improves survival, physical, and cognitive performance,

Table 5.1 Medical domain.

	Assessment	Actions if impaired
Comorbidity	History searching Long-standing diabetes complication check-up Clinical exam	Adaptation of target for blood glucose, blood pressure, and blood lipids Cancer screening Specialized advices
Renal function	Creatinine clearance	Drug-dosage adaptation Stop some treatment Search for etiology of renal impairment
Nutrition	Weight	Obesity or undernutrition check-up
	MNA	Nutritional counselling Incentive to physical activity Housekeeper for shopping and meal preparation Meals on wheel
	Oral health	Dental treatment and oral health hygiene (asialia, candidiasis, dental plaque, loss of occluding pairs)
	Swallowing test	Search for etiology Meal texture adaptation Caregiver education
Pain	Visual analogical scale External assessment	Search for etiology Analgesics with adapted dosages Physical treatment Follow-up
Pressure ulcer risk	Braden scale	Position adaptation Special equipment Nutrition and hygiene Early getting up after any immobilization
Drugs	Number Search for adverse effects and interactions Benefit/risk ratio	Treatment revision Help for treatment handling Prescribing insulin injections by nurse Patient and caregiver education

MNA, Mini Nutritional Assessment.

and reduces medications, costs, and the use of hospital facilities and institutionalization [21–23]. However, there is still some controversy in terms of its cost-effectiveness and efficacy, and certainly we know less in the geriatric population with diabetes. The only meta-analysis focused on the CGA, published in 1993, found significant heterogeneity among studies and highlighted the need to refine the CGA process in order to enhance its effectiveness and efficiency for diverse diseases in the elderly [24]. It is important to emphasize the importance of chronological age as a major risk factor for the increasing prevalence of chronic diseases and disability [25].

A Cochrane review for randomized controlled trials comparing the CGA (whether by mobile teams or in designated wards) to usual care identified 22 trials evaluating 10,315 participants in six countries. After 12 months of follow-up, the patients who received a CGA were significantly more likely to be alive and in their own homes when compared to general medical care [26]. Older patients were more likely to survive admission to hospital and return home if they underwent a CGA while in the inpatient setting. In addition, they may have improved cognitive functioning, and fewer will die or experience deterioration. Remarkably, these benefits might be cost-effective. The authors concluded that the

Table 5.2 Functional domain.

	Assessment	Actions if impaired
Functional status	IADL (instrumentals activities, among them housekeeping, budget and drugs management, phone and transportation)	Housekeeping help Budget control (family, lawyer) Nurse help for medications intake
	ADL (basic daily living activities)	Human help Technical aids
Sensory assessment	Vision, hearing	Technical aids Specialist treatment Environmental adaptation
Mobility	Mobility limitation for heavy tasks Gait speed SPPB	Co-morbidity monitoring Nutritional assessment Incentive for physical activities
Feet exam	Comprehensive clinical exam	Co-morbidity screening and monitoring Wound and infection treatment Adapted footwear
Fall risk	Clinical exam Timed get up and go test One-leg stance	Research for etiology Check blood glucose profile Physiotherapy Incentive for physical activities

IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; SPPB, Short Physical Performance Battery.

Table 5.3 Psychological/mental domain.

	Assessment	Actions if impaired
Cognition	Global: MMSE	Comprehensive memory assessment in memory clinics Check blood glucose profile
	Clock-drawing test	Implement human help for diabetes disease management Adapt therapeutic education Caregiver support and education
	Timed test of money counting	Prescribe insulin injection by nurse
Behavior	NPI	Delirium screening Check blood glucose profile Treatment revision
Depression	GDS-15 or GDS-4	Depression treatment (non-pharmacologic and pharmacologic) Adapt therapeutic education
Delirium	CAM	Search for etiology Check blood glucose profile Revision of treatment

MMSE, Mini Mental State Evaluation; NPI, Neuropsychiatry Inventory; GDS, Geriatric Depression Scale; CAM, Confusion Assessment Method.

Table 5.4 Social domain.

	Assessment	Actions if impaired
Social support	Presence of family or other caregivers Needs and abilities of caregivers	Offer patient and family education and support resources Involve family and other caregivers in the plan of care and follow-up
Economic situation	Insurance status Social and financial possibilities	Involve social worker Help to obtain financial resources

CGA increases patients' likelihood of being alive and in their own homes after an emergency admission to hospital [27].

The CGA has been widely studied, but there is no consensus on how to implement it and discrepancies have been described on how it is implemented in the outpatient setting [28]. For the geriatric population with diabetes, we propose to use four domains: medical, functional, psychological, and social [29, 30]. Even though geriatric syndromes may overlap on several domains, this structured approach may facilitate dissemination to non-geriatricians. Most providers who manage diabetes (endocrinologists, family practitioners, and primary-care providers) are trained in the assessment and management of the medical domain, but encounter difficulties when dealing with multimorbidity and polypharmacy.

Within the functional domain falls, impaired mobility, functional decline, vision loss, and hearing loss are among the most common geriatric syndromes. To explore this domain, we will briefly review the topic of falls. A true fall is defined as a person coming to rest inadvertently on a level below their prior location [31]. Falls are quite frequent in older people and are associated with a high risk of death or serious injury [32]. Falls constitute a public health problem that is largely preventable [33] and sadly is terribly under-detected. A study found that less than half of providers know that their patients are falling [34]. Falls are generally driven by a combination of intrinsic (the person's characteristics) and extrinsic (exogenous, the environment) factors. Diabetes can contribute in several ways to the intrinsic factors, including impaired neurological and musculoskeletal health on development of diabetic neuropathy and vascular disease, autonomic dysfunction and orthostatic hypotension, physical function decline, cognitive decline, and the use of medications that may lead to adverse reactions like hypoglycemia. Furthermore, reports suggest that the quality of bone in patients with diabetes is affected, making them more vulnerable to fragility fractures in the setting of falls [35].

There is limited information about the association between falls and the intensity of glycemic control, the type of agents used, and a combination of these and other factors, while there was no increased risk of falls or fractures in patients receiving intensive glycemic control in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [36]. Others have reported that patients receiving insulin therapy are at greater risk of falls (requiring hospitalization) compared to those without diabetes [37]. A fall could be a leading presentation of hypoglycemia in the elderly, but this is may not be detected unless the clinician purposely enquires about the occurrence of falls since it may lead to a life-changing injury [38]. Those at high risk of hypoglycemia should be screened for falls as a routine CGA to be added to the CDE. A comprehensive fall risk assessment may follow if falls occur more than once per year or if there are issues with gait and balance [39]. The functional domain has major implications for the dexterity and physical capacity of the patient to perform diabetes self-management (e.g., visual loss can impair the ability to read glucose results and inject insulin units). Tools such as insulin-delivery systems, with training for those with visual impairment, can be implemented to allow the person maintain independence in the management of diabetes.

In the psychological/mental domain, depression, delirium, and dementia are common geriatric syndromes. Personality disorders and addictions are increasing in prevalence in this age group. To explore this domain, we will analyze the impact of cognitive decline/dementia syndromes on diabetes. Alzheimer's disease is the sixth leading cause of death in the USA and the fifth leading cause among people aged 65 years and over [40]. Older adults with type 2 diabetes are 50–100% more likely to develop dementia than those without. Those with longer diabetes duration, poorer glycemic control, and chronic vascular complications are at the highest risk [41]. Furthermore, hypoglycemia is associated with cognitive impairment, both

acute (erratic and irrational behavior, confusion, impaired vision and balance, which can result in falls or accidents) and chronic (leading to dementia) [42]. A prospective cohort study that followed 16,667 patients with diabetes without dementia at study entry found that severe hypoglycemia was associated with greater risk of dementia [43]. Both obesity and diabetes are recognized as risk factors for cognitive decline [44]. While there is no clear pathophysiologic pathway (most likely it is multifactorial), the epidemiological links between diabetes and dementia are quite strong. Thus, the evaluation of cognitive function in older adults with diabetes is warranted, especially for those older than 70 years of age and those with longer duration of disease [45]. A diagnosis of dementia will not only help to secure proper resources and support, but also increases the understanding by providers and family that success in diabetes self-efficacy and self-management rely on the ability to understand and follow the education provided. Sadly, many older adults suffer isolation or lack of support, and many of them depend solely on themselves to manage their medications. Certainly there are several other implications that are beyond the scope of discussion for this section.

Finally, in the social domain elder abuse, social isolation, poverty, and lack of family or social support are common scenarios affecting the older person. The social network of people decreases as family and friends age and die, or become ill and dependent themselves, so they are no longer part of the support system. In the general population with diabetes, the economic costs from diabetes can be direct (management-related costs) and/or indirect (work absenteeism, reduced productivity at work and at home, reduced labor force participation from chronic disability, and premature mortality) [46]. In the geriatric older person with diabetes it is possible that the latter may be less frequent (since many have already retired), but the costs of management may actually be higher than in younger patients if we consider the natural history of the disease, which may require a greater number of medications to achieve control, as well as the development of complications and increased life expectancy [47, 48]. The economic situation can be a major constraint for those who depend on insurance status and family support, an important resource that could be more lacking in this age group.

5.3.1 CGA within the medical domain: Co-morbidity

Long-standing complications of diabetes should be reviewed and this is recommended in all patients with diabetes. Other co-morbidities must be assessed alongside a thorough clinical examination, which in turn may drive the need for further investigations. Any organ failure must be investigated. Cancers are more frequent in older people with diabetes [49] and clinical screening for these should be carried out according to standard guidelines. While this does not necessarily mean that the endocrinologist must pursue cancer screening, it would be appropriate to ensure that the patient keeps up to date with standard screening interventions conducted by his primary care physician. This will be relevant for the understanding of the patient's prognosis and survival, which then will impact his glucose targets and management.

In dependent or critically ill older patients with diabetes the increased risk of pressure ulcers [50] justifies systematic screening and preventive or curative intervention.

Pain is frequent in older people, particularly those with diabetes. It may be due to neuropathy but any other cause is possible. Thus, a comprehensive clinical assessment of neuropathic or non-neuropathic pain may improve the efficiency of antalgic treatment and minimize adverse events.

Routine biology completes the co-morbidity assessment, and should include assessment of renal function and staging of nephropathy.

5.3.1.1 Treatment revision

At the end of the CGA, targets for blood glucose, lipids, and blood pressure can be proposed based on assessment and current guidelines [51–54]. Treatment revision includes antidiabetic drugs, cardiovascular drugs, and any other medications and nutritional supplements. The aim is to reduce iatrogenic risk with the best efficacy. Therapeutic education must also be adapted to the needs and capacities of both patient and caregivers.

5.3.1.2 Polypharmacy

There are several definitions of polypharmacy related to the total number of medications, the number of medications for one condition, and the use of medications that are not justified by benefits over disadvantages. However, if polypharmacy is defined as more than four

medications, it is frequent and often unavoidable given the standard-of-care for diabetes treatment [55]. Polypharmacy leads to increased costs and non-adherence [56], and non-adherence can lead to uncontrolled glycemic control. Increased economic costs lead to mental preoccupation/anxiety as well as socioeconomic burden.

The endocrinologist may not be in charge of fixing all polypharmacy, but could start by addressing if the patient knows what and why he/she is taking a medication, advise against non-required over-the-counter medication, and strongly recommend a return to the prescribing provider. This may facilitate diabetes control and help with the patient's adherence.

5.3.1.3 Nutritional assessment

Diabetes is associated with obesity as we age [57]. Obesity itself affects all four geriatric domains and if left untreated leads to a vicious cycle of progressive deterioration of physical activity and function, worsening of diseases, further weight gain, and further worsening of the metabolic state [58]. Consequently, the success of diabetes management will be challenged by the persistence of such negative scenarios in the geriatric population.

The level of malnutrition risk is similar in subjects with diabetes residing in the community [59] and in inpatients in hospital [60]. It has even been shown that diabetes in stroke patients is a risk factor for malnutrition, probably due to dietary restriction and higher rate of dysphagia [61]. Oral health and swallowing capacities must be checked. In particular, oral candidiasis must be investigated and treated, and the patient referred to a dental surgeon. Any proposed diet must be adapted to nutritional risks, using meal texture adaptation, meal enrichment or oral supplement. The diet should also be tailored for the lowest risk in association with antidiabetic medications. Physical activity advices adapted to physical limitations or not are proposed to improve nutritional status.

5.3.2 CGA within the functional domain

The mobility scale assesses capacities to perform heavy tasks without help, such as walking up and down a flight of stairs, walking half a mile without stopping or doing heavy housework [62]. Walking speed, strength, balance, and the risk of falls ought to be assessed.

The timed up and go (TUG) test (time taken to rise from a chair, walk 3 m, return, and sit down) and the one-leg stance (OLS) test (time taken to stay in equilibrium while standing on one leg) are used to predict the risk of falling [63].

The Short Physical Performance Battery (SPPB) explores balance, strength (chair rise), and gait speed [64]. The maximal score is 12, and from 10 to 12 the subject is considered as having a high physical performance level. It is tailored to provide an accurate measure of physical performance of frail or pre-frail subjects and has been used as an efficacy criterion for disability prevention through various interventions.

In subjects with a history of falls, the Berg scale provides a detailed assessment of balance and is used to drive physiotherapist intervention. Strength can be measured with a dynamometer or indirectly assessed by performance in a chair rise time test.

The foot examination is a regular section of the CDE. However, further assessment would look for neuropathy, occlusive arterial disease, infections, swelling, and wounds. Beneficial outcomes may range from improvement of blood glucose control, anti-fungus treatment, adapted footwear, wound treatment, and monitoring. These interventions may improve gait and function. Urinary incontinence is frequent in people with diabetes and may be improved with better blood glucose control (with less glycosuria and less urinary infection risk).

The Instrumental Activities of Daily Living (IADL) assessment [65] explores capacities to live in an autonomous way at home. The Activities of Daily Living (ADL) assessment [66] explores the actions needed to take care of basic needs without help.

Dependency in the IADL assessment is mainly associated with cognitive troubles. Particular attention should be given to the capacity to self-manage medications. The care plan can be adjusted based on the outcomes from this assessment.

Sensory loss, particularly but not only visual loss, can impact diabetes self-management and self-efficacy. When detected, referral to a specialist and subsequent intervention may facilitate the management of diabetes in the older person.

5.3.3 CGA within the psychological/mental health domain

The assessment of mental health includes cognition, behavior, and affect. In addition, depression and dementia are frequent in older patients, particularly those with diabetes [67, 68], therefore screening is very important.

In a stable condition, the Mini Mental Status Examination (MMSE) [69] allows a global assessment of cognition. Age, socio-cultural and educational variables [70], sensory loss, anxiety, and depression should be taken into account for interpretation. The test should be performed in patients without asthenia or alertness troubles. In this latter situation, the MMSE should be repeated at a time interval after the episode. It is not easy to propose universal MMSE thresholds for dementia diagnosis because the predictive positive value depends on epidemiological parameters, among them the prevalence of dementia in the given population in addition to those above. A lowering in activities of daily living associated with a lower MMSE score indicates the need to refer the patient to a specialized memory clinic, where the diagnosis of dementia syndrome can be confirmed and the etiology pursued. A diagnosis of dementia was shown to be associated with an increased frequency of hypoglycemia [71] and thus is a very important factor when considering the care plan and therapeutic objectives.

Self-managing of diabetes requires good cognitive functioning, particularly regarding adequate executive function. The clock-drawing test has been proposed to test the ability of older patients to self-manage [72]. In insulin-dependent diabetes, the Timed Test of Money Counting [73] has been proposed to test the ability for insulin self-injection. The patient has to count money: one 5 euro note, two 1 euro coins, one 2 euro coin, one 50 cent coin and three 10 cent coins. The threshold for the ability to self-inject insulin was defined at 45 seconds to complete the count. The assessment of cognition has certain implications in self-efficacy, and its assessment is supported by the need to involve the patient in the care plan and therapeutic management. In older patients the caregiver should be included in the educational process.

Behavior assessment may be particularly interesting in subjects with cognitive troubles. The Neuropsychiatric Inventory (NPI) records 12 symptoms, their severity, and their burden on the caregiver [74]. Apathy was found more frequent in older people with diabetes compared to others [75]. Apathy is associated with cognitive decline, depression, and higher levels of HbA1c. Unexplained behavior changes may result from unrecognized hypoglycemia and sometimes hyperglycemia. The response of detected behavior troubles to care plan revision should be followed.

When the patient is hospitalized or when a fluctuating situation is reported, delirium symptoms should be searched and DSM IV criteria filled in. The Confusion Assessment Method (CAM) [76] can be used to screen for delirium. In this case, the glycemic level should be checked first. Other causes of delirium should be also considered in this multifactorial condition and treatment revision should be done.

In the CGA, depression screening is performed using a robust scale, usually GDS 15 or GDS 4 [77]. Depression is seen in one in four older patients with diabetes [67]. Insulin resistance increased the risk of developing depressive symptoms in older men [78]. Moreover, the rate of depressive symptoms may be related to ischemic lesions, as evidenced by magnetic resonance imaging [79]. Depressive and anxiety symptoms may interfere with the self-care behavior of patients with diabetes [80] and thus this should be considered. Furthermore if depression is detected, the patient should be treated accordingly, which includes non-pharmacological and pharmacological interventions.

5.3.4 CGA within the social domain

Older patients with diabetes need social support. The needs of patients and their caregivers, if any, should be evaluated to construct the care plan. Social difficulties impair health-related quality of life and increase the risk of functional dependency [81]. CGAs take different forms according to the global health status of the older patient and according to the living situation, that is, home-living, hospitalization or admittance to an emergency department for an acute event [82], or admission to a nursing home.

5.4 Conclusion

Diabetes management in the elderly population is often difficult because of impairment of their physical, psychological, and cognitive functions, and the lack or shortage of family or social support.

Furthermore, many aspects of the disease, including pathophysiology, diagnostic criteria, dosing and side effects of medications, dietary consideration, exercise strategies, and impact of the disease on quality of life, require special considerations [83].

Beyond the dreaded diabetic complications, attention must be given to age-related co-morbid conditions

called geriatric syndromes. Elderly diabetic patients may have increased risk for functional dependency and frailty, therefore a comprehensive geriatric assessment may be a necessity in the treatment of elderly patients [84].

The involvement of a geriatrician in clinical care becomes important to provide scientific evidence that would support CGA being implemented in subpopulations of older people with chronic conditions. Incorporating a tailored CGA and screening for geriatric syndromes in the right patient will not only contribute to the proper management of diabetes in the geriatric patient, but may also be indicated to actually provide good clinical practice.

We are not aware of any study yet that addresses the cost-effectiveness of the CGA in the geriatric patient with diabetes, and further studies are needed to support its dissemination. The CGA should complement the understanding and management of diabetes in this vulnerable population.

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SECTION B

Vascular risk factors and complications

CHAPTER 6
Peripheral arterial disease

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KEY MESSAGES

- Peripheral arterial disease is a frequent complication in older people with diabetes, with the risk exacerbated by the presence of hypertension, smoking, hypercholesterolemia, and advanced age.
- Peripheral arterial disease is often asymptomatic (subclinical disease) or may show as a non-specific presentation like tiredness or functional impairment.
- Peripheral arterial disease is linked to increased mortality, as well as a higher risk of other atherosclerosis manifestations like myocardial infarction or stroke.

6.1 Introduction

Peripheral arterial disease (PAD) is a condition often ignored, under-diagnosed, and usually poorly treated in the daily practice of medicine. This reality is even greater in the elderly, in whom the typical symptoms of PAD (pain, claudication) only appear in less than 30% of cases. In addition, these symptoms can be mistaken for other symptoms attributable to diseases very prevalent in the elderly, such as osteoarthritis or neuropathy.

Very often, as is typical in older patients, the only manifestation of the disease is the loss of function, translated into a progressive loss of autonomy for performing the activities of daily life. The actual prevalence of PAD in older populations is not known, making it even more difficult to know in what percentage of cases of gait disorders and/or falls the underlying cause (or adjuvant cause) is PAD. Accordingly, clinicians need a high index of suspicion if they accept PAD as a cause of functional impairment and falls in older patients. Its relatively benign evolution is another reason that leads us to ignore this disease. Traditionally, there has been less importance attached to PAD than coronary disease or brain vascular disease for not compromising key organs, such as the heart or brain. This has led us to ignore the serious consequences of the evolution of PAD, including amputation, and the serious prognostic implications of the presence of atherosclerotic lesions in the legs. PAD mortality at 5 years is higher than that for cancers, around 30%. The majority of these patients die of vascular complications that do not occur in the lower limbs, but in coronary and cerebral territories. Recent studies suggest that the risk of a vascular event in any territory is approximately twice as high in patients with PAD as in patients with coronary or cerebral vascular involvement. For this reason, in recent years PAD has become an important marker of cardiovascular risk, allowing the identification of subjects with very high cardiovascular risk, who require intensive treatment of risk factors to delay the risk of functional impairment.

6.2 Epidemiology of PAD

It is worth reminding ourselves that atherothrombosis, directly or indirectly, accounts for 70% of all deaths in people over 70 years. The factors that lead to atherosclerotic disease are multiple: genetic factors, metabolic diseases, inflammatory diseases, lifestyle, and local and

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systemic conditions of the vascular system. Contributing risk factors are age, smoking, hypertension, dyslipidemia, type 2 diabetes mellitus, physical inactivity, and abdominal obesity. The INTERHEART study showed that nine of these factors were responsible for 90% of cardiovascular diseases, age being the only unmodifiable factor.

Age is also the main risk factor for PAD. Other risk factors besides age are smoking, diabetes, hypertension, dislipemia, and hyperhomocysteinemia. Furthermore, smoking not only predisposes to the development of PAD but also increases the severity of it and affects the prognosis of revascularization interventions. A recent study, the MERITO I study, evaluated the prevalence of the low ankle brachial index (ABI) in older patients with metabolic syndrome and the risk factors associated with its development. The study showed that in patients with metabolic syndrome, the factors associated with low ABI (below 0.9) were age, higher serum creatinine levels, and presence of proteinuria. After multivariate adjustment, only age and active tobacco use continued to be significantly associated with a low ABI [1]. Diabetes mellitus is not only a qualitative risk factor but also a quantitative one. Observational studies have shown that the impact of diabetes as a co-morbid condition in patients with PAD is significant, both clinically and economically. Diabetes increased the length of stay by 5 days in patients with PAD and incurred greater inpatient costs, averaging US$1,912 more per episode of admission and a total of US$528,029 over 18 months [2].

Although arterial hypertension contributes to a lesser extent than age and active tobacco use to the development of PAD, it is also a risk factor that needs to be controlled. With respect to dyslipidemia, it seems that the ratio of total cholesterol/high cHDL is the best predictor of PAD and anti-lipid lowering therapy treatment has been shown to reduce the progression of the disease and therefore the risk of developing critical ischemia. Alteration in the metabolism of homocysteine is an important risk factor for atherosclerosis, but probably the role for this risk factor is age-dependent, being relevant in young people but not older people.

The prevalence of PAD in older people (those aged 70 years and over) is 15–20%, although it is likely that this figure would be even higher if we had more data from healthy older controls for comparison.

Patients with PAD have higher cardiovascular mortality and some recent studies have shown that in patients with PAD who are over 75 years of age, mortality rates were 38% in individuals without diabetes and 52% in individuals with diabetes [3]. In addition to this role of PAD as an overall predictor of cardiovascular risk, the ABI is a marker of subclinical functional decline, as shown by Guralnik *et al.* [4]. That study demonstrated that compared with participants without PAD, asymptomatic PAD was associated with greater mean annual decline in 6-minute walk performance and an increased odds ratio for becoming unable to walk for 6 minutes continuously, both of which are markers of functional decline.

6.3 Pathophysiology

Atherosclerosis is the process of thickening and stiffness of the arteries, whose basic lesion is the atherosclerotic plaque. Until recently, the classic idea of atherosclerosis was the mechanical accumulation of lipids and a fibrodegenerative response of the arterial wall because of changes in its structure, which caused a progressive failure of tissue perfusion. The concept of inflammation has been added to this idea, making atherosclerotic disease a true multifactorial disease in which metabolic, inflammatory, hemodynamic, and hemostatic factors, with both local and systemic roles, are involved.

There are many studies that have evaluated the role of inflammation and its relationship to various acute phase proteins, particularly C-reactive protein (CRP), with PAD. Apart from CRP, other circulating biomarkers, such as matrix metalloproteinases (MMPs), selectins, and interleukin (IL)-1, IL-2, IL-6, IL-8, and IL-10, are not only markers of inflammation but also play an active role in peripheral atherogenesis.

CRP is one of the best known markers of inflammation. It is derived from leukocytes in response to IL-6 stimuli and is involved in the release of endothelial monocyte chemoattractor protein-1 (MCP-1), which in turn attracts monocytes towards the endothelial barrier and upregulates the release of the tissue factor and other pro-inflammatory cytokines added to inhibit the release of nitric oxide (NO) [5].

MMPs play a role in the development of arterial lesions and also in facilitating monocyte invasion. High plasma levels of MMPs have been found in patients more prone to arterial damage, such as patients with type 2 diabetes and PAD.

Selectins, including E-selectins, L-selectins, and P-selectins, are a family of type-1 cell surface glycoproteins. These selectins were the focus of a study carried out on patients with PAD with or without type 2 diabetes. The results revealed high plasma levels of E-selectin, suggesting the involvement of selectins in the activation process of endothelial cells, which is crucial in the atherogenic process.

Although the role of interleukines in the generation of atherosclerosis is not well understood, recent progress in the physiopathology of PAD has highlighted inflammation as a key contributor [6]. Circulating biomarkers, apart from CRP, such as MMPs, selectins, IL-1, IL-2, IL-6, IL-8, and IL-10, are useful for the clinical characterization of PAD. In fact an increasing body of evidence supports the notion that several circulating biomarkers are associated with the main aspects of PAD. Current data indicate that the appropriate use of biomarkers in patients with PAD may contribute to an early diagnosis, an enhanced knowledge of the developmental process of the disease, and the subsequent improvement of current therapies and the development of new ones [6]. In the type 2 diabetes population biomarkers such as fibrinogen and CRP have been related to the progression of peripheral atherosclerosis and might be implicated in predicting the clinical course of PAD in the type 2 diabetes population [7]. Other studies have also studied the most specific biomarkers, comparing their levels in patients with PAD with those in patients with other atherosclerosis diseases, for example coronary heart disease. This is the case of MMP-9, IL-6 among IL, adiponectin, ICAM-1, osteoprotegrin, and CD-40 ligand. Many of these are expressions of the high inflammatory burden observed in patients with PAD [8]. However, additional studies on this matter are required to develop clinically useful markers of PAD by using novel approaches, such as proteomics [6].

In the same way, advanced glycosylation end-products (AGEs) play a crucial role in the development of PAD in older people with diabetes. AGEs levels are increased in type 2 diabetic patients with PAD as compared with those levels in diabetic patients without PAD and control subjects. More precisely, among AGEs components, pentosidine appears to be strongly associated with the peripheral artery status of diabetic patients. In addition, lipid oxidation, estimated by the serum levels of malondialdehyde (MDA), is associated with diabetic peripheral angiopathy. On the other hand, both total reactive antioxidant potential (TRAP) and vitamin E levels, as expressions of a defence mechanism against glycolipid oxidation, are lower in type 2 diabetic patients with PAD than in those diabetics without PAD and in healthy subjects [9].

The evolution of atheroma includes several stages following the breach (harmful lesion) (see Figure 6.1) but unfortunately this complex process is not continuous or ordered because even if the injuries are developed gradually, the first symptom of an injury occurs suddenly. It is essential to detect physiological disorders associated with endothelial dysfunction and its progression toward atherothrombosis before they are visible obstructive lesions, which highlights the importance of the early treatment of vascular risk factors. It must be remembered that vascular disease is not simply a local process in a concrete plaque, but a widespread process that affects the entire vascular tree. This concept has therapeutic implications because it forces us to use an integrated treatment. Another important aspect of the pathophysiology of atherosclerosis in the elderly, and more specifically of endothelial dysfunction in the elderly, is which processes that occur at the endothelium are attributed to physiological aging and which to the presence of other cardiovascular risk factors. In fact some of the mechanisms involved in the development of endothelial dysfunction are shared by both aging and cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia) [10].

Peripheral arterial insufficiency occurs when the blood flow reaching limbs is insufficient to fulfill the metabolic necessities of the tissue. It often arises from the presence of an occlusive arterial disease, with the underlying disease process being atherosclerosis, which affects primarily, but not exclusively, the vascularization of the lower limbs.

Atherosclerosis, and in particular the formation of atherosclerotic plaque, is an universal process, although it shows some pathophysiological differences depending on anatomic location. Atherosclerotic plaque located in high-risk lower limbs may be associated with a hypercoagulable state, giving rise to an acute event. By contrast, in the coronary arteries atherosclerotic plaque consists of a large extracellular lipid core and a large number of foam cells, coated with a thin cover susceptible to breakage, which is the ultimate cause of the acute event that happens. There is a common consequence of all these injuries: an imbalance between the needs of the tissues

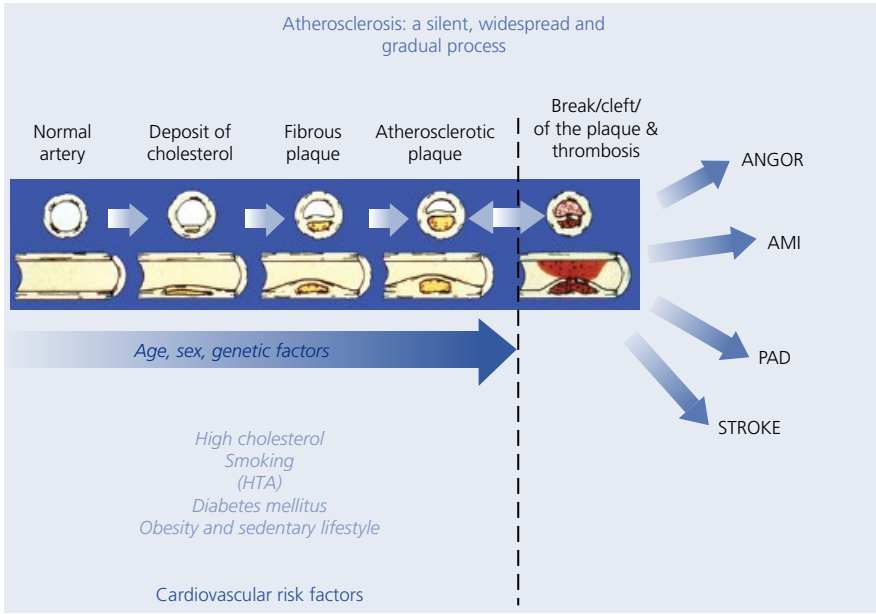

Figure 6.1 The evolution of the atherosclerosis.

and blood flux. If this mismatch occurs suddenly, as in the thrombotic event, it will lead to acute ischemia. If the establishment of the stenosis is gradual, allowing the development of collateral circulation and metabolic adaptation of the muscle mass of non-ischemic muscle groups, ischemia may persist as a chronic state (Figure 6.1).

From the pathophysiologic point of view, we can say that functional ischemia exists when blood flow is insufficient to satisfy the demand caused by exercise but it is enough at rest. This state of functional ischemia translates clinically into intermittent claudication. The critical ischemia occurs when the flow is insufficient even at rest, appearing pain and trophic lesions in the extremities. In this situation there is a need to intervene to restore adequate blood flow, to avoid the risk of amputation. However, the symptoms will largely depend on the number of affected areas and the level of physical activity the subject develops.

The presence of several cardiovascular risk factors, which act in a synergistic way, is the main condition for progression of the disease and amputation. However, not all cardiovascular risk factors contribute equally: diabetes mellitus multiplies by four the risk of critical ischemia, smoking increases it by three, and an ABI less than 0.5 by 2.5 times. In the case of amputation, there are also other independent risk factors: sensory neuropathy, PAD, previous minor amputations, and using insulin [11].

In the Wisconsin study, which followed a cohort that included elderly patients for 14 years, the factors associated with a greater need to amputate were being male, high levels of HbA1c, high pulse pressure and severe retinopathy, while regular aspirin consumption was protective [12].

In addition, other factors prevalent in the elderly (physical disability, loss of vision or a shortage of social resources) act as facilitators of its genesis. However, in the pathogenesis of diabetic amputations in the elderly coexisting involvement of the peripheral nervous system, microvascular damage, and infection are the most important concurrent factors. Peripheral neuropathy diminishes algesic perception, placing skin at risk from harmful forces and muscle atrophy. As a consequence, changes in the sites of pressure points occur, with consequent excessive pressure being applied to sites unprepared. Sensory neuropathy hinders the perception of pain as a symptom of alarm, thereby facilitating the emergence of pressure ulcers. Autonomic neuropathy facilitates the opening of artery–vein shunts and risks inadequate skin hydration.

The relevance of the involvement of microcirculation has been widely discussed. Despite the existence of a thickening of the basement membrane, this factor does not appear to be of clinical significance in the absence of peripheral and autonomic neuropathy. Other factors, directly and indirectly related to vascular injury, contribute to the development of clinically apparent damage: ischemia causes pain, especially in patients with high blood glucose, difficulty in healing existing injuries, and delay in the sterilization of infected lesions. Other mechanisms that can hinder healing include AGEs or zinc shortfall in relation to its increased renal elimination in patients with poor glycemic control. It is quite possible that this mechanism is enhanced in the elderly. The ischemia also hinders the delivery of antibiotics to the infected ulcers.

Finally, other mechanisms associated with hyperglycemia may participate in the pathogenesis of diabetic foot, but their role is more controversial. This is true for the decline in chemotaxis, phagocytosis, and bacterial lysis secondary to hyperglycemia [13].

In older people amputation remains a dramatic complication because it is associated with disability and psychological damage, but a major cause of functional decline, particularly in the presence of sarcopenia, is PAD, which will be discussed next.

6.4 Clinical presentation

6.4.1 Asymptomatic

Although intermittent claudication is the most characteristic symptom in patients with PAD, the majority of individuals with this pathology do not experience this typical limb ischemic symptom. Some studies from the 1990s [14, 15] showed how intermittent claudication underestimates the prevalence of PAD. Although the underlying reasons for symptom production are not well known, it depends on endothelial function (an independent predictor of symptom severity), development of collateral arteries, muscular adjustment to the ischemia, and employment of the muscular groups least affected [16]. Added to this, the presence of co-morbidity and functional impairment in some elderly patients does not allow them to have an active enough life to provoke the intermittent claudication [17]. Multiple studies have shown that patients with a low ABI but without claudication are characterized by slow walking, longer time to rise from a seated position than normal, poor standing balance score, and fewer blocks walked per week, even after making adjustments for age, sex, race, cigarette smoking, and co-morbidities [4, 18]. Other papers demonstrate that people with PAD who never experience claudication symptoms have not just poorer functional performance but also poorer quality of life and more adverse calf characteristics compared with patients with intermittent claudication [19]. These consequences predict later increased mobility loss and mortality [20–22]. All this research demonstrates that functional impairment is a frequent and important contributor to the clinical presentation of PAD in older people, and highlights the need for a change in the clinical approach to increase early detection of these patients [23].

6.4.2 Claudication

Less than 20% of patients with PAD report the typical symptoms of intermittent claudication, defined as fatigue, discomfort or pain which occurs in specific limb muscle groups during effort due to exercise-induced ischemia [24]. These symptoms are absent at rest. It is important to make a differential diagnosis to that for other causes of ischemia (emboli, Buerger's disease, other arteritides), and it especially must be distinguished from other illnesses that cause exertional leg pain, so-called "pseudoclaudication" (lumbar disease and spinal stenosis, osteoarthritis, severe venous obstructive disease, peripheral neuropathy) [25]. The anatomic site of arterial stenosis has frequently been associated with specific leg symptoms. For example, obstructions in the femoral and popliteal arteries are associated with calf pain, and affected tibial arteries could produce calf pain, foot pain or numbness. Occlusive disease in the iliac arteries could produce hip, buttock, thigh, and calf pain [24].

The severity of the clinical symptoms allows us to classify patients with PAD into several categories (Table 6.1). This is useful to facilitate communication between different specialists and is of important therapeutic value. Although intermittent claudication often has a poor correlation with actual stenosis, the symptoms, their repercussion on quality of life, and the potential benefits with different treatment strategies are important in deciding between revascularization and conservative treatment [25].

Table 6.1 Fontaine's stages.

Stage	Clinical
I	Asymptomatic
IIa	Mild claudication (more than 150 m)
IIb	Moderate-severe claudication (less than 150 m)
III	Ischemic rest pain
IV	Ulceration or gangrene

6.4.3 Critical limb ischemia

Critical limb ischemia is defined as limb pain which occurs at rest or immediate limb loss that is caused by a severe compromise of blood flow to the affected extremity [24]. Pain typically occurs at rest and it worsens (or aggravates) when the patient is supine or when the leg is in a higher position than the rest of the body. It improves in a lower position, and it can produce unpleasant dream states, requiring the use of narcotic medications in addition to analgesia to treat these patients. These patients can also suffer trophic skin changes or tissue loss, ulcers and gangrene. Ischemic ulcers are very painful (until neuropathy develops when symptoms may subside), with irregular margins, no pulse, dry, and frequently occur on toes which are cold and pale or display cyanotic skin coloration. The ulcers usually are associated with infection in the surrounding tissue.

The progression of PAD from asymptomatic and intermittent claudication to critical limb ischemia may occur gradually. However, sometimes a fast or sudden decrease in limb perfusion threatens tissue viability. In this case, the critical limb ischemia may be the initial presentation of a lower extremity PAD. This event is more frequent in elderly diabetic patients. This occurs because arterial disease often develops in small arteries [16], which may cause further co-morbidity. Pain, paralysis, paresthesias, pulselessness, and pallor are the five "Ps" that suggest this syndrome. In this case it is imperative to give the patient an emergency evaluation by a vascular surgeon.

6.4.4 Diabetic foot

The term "diabetic foot" is taken to encompass any foot lesion occurring as a result of diabetes and its complications [26]. It carries high morbidity and mortality, and represents the most common cause of hospitalization in patients with diabetes. Frequencies of amputation and ulceration vary considerably as a consequence of different diagnostic criteria as well as regional differences. Up to 25% of patients with diabetes will develop a foot ulcer sometime during their lives, with an annual incidence of around 2%. Up to 2% of these patients may already have undergone amputation. It is estimated that risk of a person with diabetes undergoing a lower extremity amputation is 23 times that of a person without diabetes. Diabetes remains the major cause of non-traumatic amputation in most western countries; rates are as much as 15 times higher than in the non-diabetic population [26, 27].

More than 85% of amputations are preceded by an active foot ulcer. PAD is an independent risk factor for subsequent ulceration and limb loss in diabetes. 50% of patients with diabetic foot ulceration have been diagnosed with PAD and its presence is a marker of poor prognosis: patients with PAD are less likely to heal and more likely to require amputation compared to patients without PAD [27].

6.5 Diagnostic methods

6.5.1 Anamnesis and physical assessment

Diagnosis of PAD is based mainly on clinical evaluation: medical history and physical examination [24]. Often patients minimize their symptoms, attributing them to normal aging. Because of this an active investigation of asymptomatic or atypical presentation of PAD must be done [23]. A careful history, including a CGA, can uncover a functional impairment when this is the clinical presentation. Clinical guidelines for type 2 diabetes mellitus (European Diabetes Working Party for Older People) [28, 29] suggest that a CGA should be a routine measure in older people with type 2 diabetes at diagnosis and at regular intervals, and recommends as a minimum an annual inspection of the feet by a healthcare professional, including a vascular and neurological examination, even if symptoms are not pressent. The physical assessment should include an examination with shoes and socks off, paying special attention to pulses (femoral, popliteo, posterior tibial, and pedal), bruits, hair loss, skin color, temperature, ulcers, and trophic skin changes [25].

Physical measures like slow walking velocity, gait variability, longer time to rise from a seated position, weakness or poor standing balance score have been related to the presence of subclinical disease [4, 21, 23]. For this reason, functional assessment should be included in any clinical evaluation of elderly patients to detect any change in functional performance over time, such as early impairment manifestation [23]. The 6-minute walk test, which has excellent test/re-test reliability, is a well-validated measure of functional impairment in people with PAD [30].

6.5.2 Vascular diagnostic techniques

These tests allow us to establish the diagnosis of PAD objectively, to quantify the severity of the disease, to localize the stenosis, to organize a plan of treatment, and to determine the progression of disease or its response to treatment [24].

The ABI is a quick and cost-effective tool that acts as a screening method, a diagnostic aid, and follow-up mechanism [31]. To calculate the ABI, systolic pressures are determined in both arms and both ankles with the use of a hand-held Doppler instrument (see Figure 6.2). The ABI has been validated against the "gold standard", the lower extremity contrast angiography. When the ABI is <0.9, it has a sensitivity of >95%, and specificity close to 100% for diagnosing PAD [31]. In patients with incompressible arteries, such as long-term diabetics and very elderly patients, the ABI may not be accurate, raising the possibility of obtaining false negatives. In these cases alternative non-invasive diagnostic tests (toe-braquial index, exercise ABI test, pulse volume recording) should be performed [24]. Diabetic individuals with clinically suspected PAD, and those with low and high ABIs are at higher risk of cardiovascular death, but a linear relationship has been demostrated between toe-braquial index and cardiovascular death irrespective of diabetes status [32]. Altered ABI has been associated with systemic atherosclerotic disease, total and cardiovascular mortality, and functional impairment [31, 33, 34]. The American Diabetes Association has suggested in a consensus statement, based on observational epidemiology, that

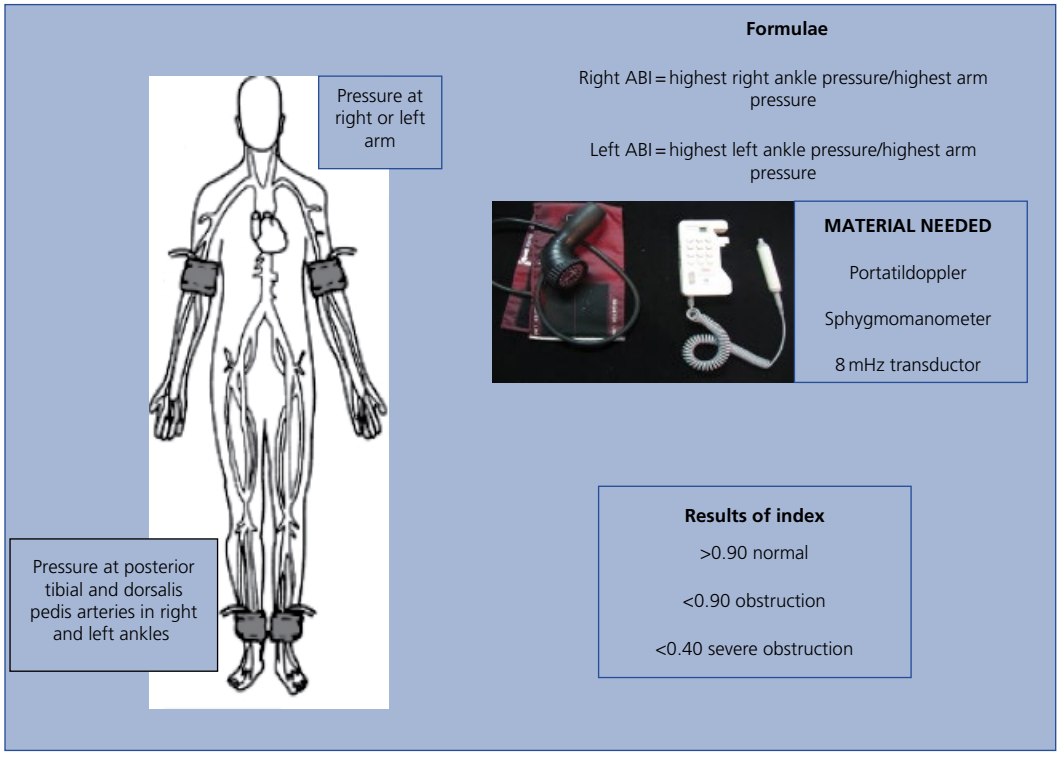

Figure 6.2 The ankle-braquial index.

ABI must be performed in outpatient departments in all patients with diabetes who are 50 years or older (i.e., in every older patient), in diabetic individuals younger than age 50 who have other atherosclerosis risk factors, and in patients who have had diabetes for 10 years [35]. In the future, these criteria can be established by randomized clinical trials or cost-effectiveness analysis in different population subgroups [31].

Other possible techniques, apart from ABI, are magnetic resonance angiography and computed tomographic angiography. These techniques are used to find the anatomic location and degree of stenosis. They are useful in selecting patients as possible candidates for endovascular treatment. The diagnostic performances of both these image procedures are quite similar and computed tomographic angiography is prefered when resonance is contraindicated. At the present time, contrast angiography is the "gold standard". It is the definitive method before revascularization procedures. Although it is a relatively safe procedure, it is associated with a higher risk of medical complications (bleeding, infection, contrast allergy) than non-invasive techniques and must be performed only in selected patients (surgical patients) [24].

6.6 Treatment

Treatment of PAD is based on cardiovascular risk factor modification, medical therapies for improvement symptoms, exercise programs to improve cardiovascular health, and functional performance and endovascular revascularization [36].

6.6.1 Cardiovascular risk reduction

Treating patients with PAD requires each modifiable risk factor that is associated with illness development and evolution to be addressed: cigarette smoking, diabetes mellitus, sedentary life, dyslipemia, and hypertension [25]. There is no conclusive evidence about the relation between control of the risk factors and PAD prognosis. Nevertheless, the role of the control of cardiovascular risk factors in the manifestation of atherosclerosis is well established and the association between PAD and systemic artherosclerosis is also established. In addition, cardiovascular events are the major cause of death in patients with PAD and require treatment of all cardiovascular risk factors as a priority in all patients with PAD, independent of their clinical manifestations.

There is little evidence about what is the best level of control of cardiovascular risk factors in elderly diabetic patients with PAD. Because of this the treatment goals are similar to those in diabetic elderly patients [24].

Antiplatelet therapy with aspirin, in daily doses of 75–325 mg, reduces the risk of vascular death, myocardial infarction, and stroke in patients with PAD [37]. Although clopidogrel appears to be more effective than aspirin in preventing ischemic events in individuals with symptomatic PAD [38], the size effect does not allow a broad recommendation about its use instead of aspirin to be made. Thus, the more expensive thienopyridines (ticlopidine and clopidogrel) may be considered as the alternatives to aspirin when patients do not tolerate the latter. Current data do not show an advantage of dual antiplatelet therapy over single-agent therapy.

6.6.2 Medical therapies for improvement symptoms

Cilostazol is a phosphodiesterase type 3 inhibitor with vasodilator and antiplatelet properties. The walking distance is increased by about 50% with cilostazol (100 mg twice a day), as compared with placebo, after 3–6 months of therapy [39]. One paper has also shown that in patients undergoing lower extremity revascularization, cilostazol use was associated with improved 1-year freedom from amputation, including patients with renal failure and diabetes mellitus [40]. Cilostazol is contraindicated in patients with heart failure, thus limiting its use in older people with diabetes, where heart failure is very common. Pentoxifylline is another drug approved by FDA for intermittent claudication, but it is considered second-line therapy because its efficacy is not well established (improvement in walking performance is comparable to placebo) [23]. This is also the case for the other commonly used pharmacological treatments (oral vasodilator prostaglandins, vitamin E, ginkgobiloba).

6.6.3 Exercise programs

The evidence supporting the beneficial effects of exercise is robust [41]. The intervention evaluated was regular walking in a supervised claudication exercise program. This improves the walking time free of pain by an average of 150% (74–230%). This occurs when the programme is developed according to certain specifications: the patient walks close to maximum tolerable pain for more than 30 minutes per session at least two or three times per week for more than 6 months [41].

Because of the difficulty many patients experience in gaining access to supervised treadmill exercise, new interventions are being evaluated [23]. Data are mixed about unsupervised exercised (home-based walking exercise) compared to supervised exercise, but its efficacy is greater compared to usual care. There are also promising results with ergometric exercise [23]. Exercise did not improve the ABI and was inconclusive on mortality, amputation, and cardiovascular events due to limited data, but it improved functionality at 3 and 6 months [41].

6.6.4 Endovascular revascularization

Endovascular or surgical revascularization therapy is reserved for patients whose functional capacity is compromised only by clinical symptoms of EAP (not other co-morbidities), patients who do not have a response to exercise and pharmacotherapy, and patients for whom the risk–benefit ratio with revascularization is favorable [24]. These patients and patients with critical and acute limb ischemia should be referred to a vascular surgeon.

Recently, some studies have shown the role of stem or progenitor cells in vascular disease, including atherosclerosis (especially critical limb ischemia) and post-angioplasty restenosis. Although these therapies are used not just in animal models but also in clinical settings closed to research units, this investigation line constitutes mainly a future approach in the treatment of PAD [42, 43].

6.7 Conclusions

An important consideration during a full evaluation of an older patient with diabetes is the detection of PAD when symptoms may not be obvious. Various methods are routinely available to assist in the diagnosis. The link between PAD and functional impairment is strong, further supporting a greater emphasis by the clinician on this macrovascular complication of diabetes.

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CHAPTER 7
Coronary heart disease

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KEY MESSAGES

- Diabetes mellitus has been recognized as an independent major cardiovascular risk factor since the publication of the Framingham study in 1979. It remains the main cause of mortality, affecting about 50–75% of all deaths in patients with diabetes.
- Diabetes itself, in the absence of associated cardiovascular disease, presents a risk of death similar to that of non-diabetic individuals with a previous history of myocardial infarction.
- Aging itself leads to stiffening of the vascular wall and loss of compliance of the aorta and major arteries.
- The mechanism of atherosclerosis in diabetes is multifactorial in origin, including endothelial dysfunction, hypercoagulability, and platelet dysfunction.
- Older patients with diabetes have a higher baseline cardiovascular risk and therefore are likely to benefit more from risk reduction than younger patients without diabetes.
- Targeting of risk factors such as hypertension, hyperlipidemia, and the procoagulant state as well glycemia is essential, necessitating a multifactorial intervention and comprehensive approach.

7.1 Introduction

Diabetes mellitus has been recognized as an independent major cardiovascular risk factor since the publication of the Framingham study in 1979 [1]. In spite of the various known metabolic and microvascular complications of diabetes, cardiovascular disease (CVD) remains the most common cause of death in all age groups [2]. In that sense, diabetes is considered as a "coronary risk equivalent" and any prevention in this population should be considered as a secondary prevention. In fact it may be appropriate to say that diabetes is a CVD. On top of that, when individuals with diabetes develop coronary heart disease (CHD) they have at least a two-fold excess risk of morbidity and worse cardiovascular outcomes compared to individuals without diabetes. Moreover, myocardial ischemia due to coronary atherosclerosis is commonly silent in those with diabetes. As a result, CHD is often present before ischemic symptoms occur. Hyperglycemia, insulin resistance, hyperinsulinemia, and visceral obesity, in addition to traditional risk factors, are the major contributors to CVD in people with diabetes. Age is another cardiovascular risk factor and directly associated with atherosclerosis [1]. This chapter reviews the synergistic effects of aging and diabetes on the vasculature, and the prevention and management of major risk factors for CHD in older people with diabetes.

7.2 Effect of aging and diabetes on the cardiovascular system

Aging and diabetes have a profound effect on cardiovascular system structure and function. These synergistic aging- and diabetes-related changes on the cardiovascular

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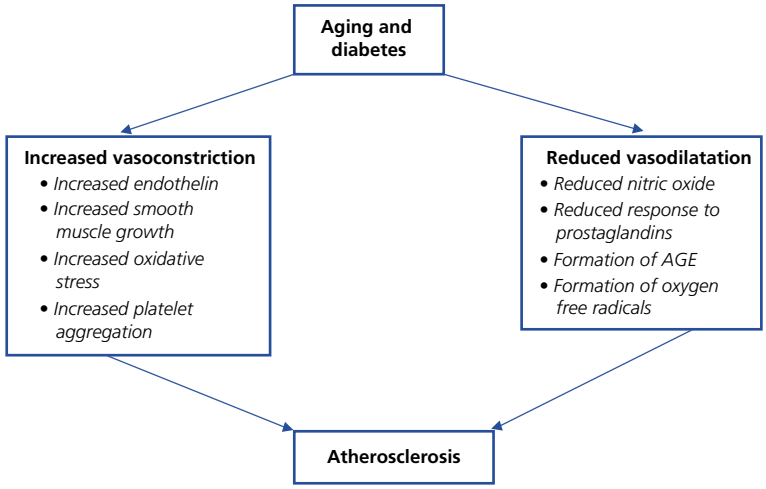

Figure 7.1 The synergistic effects of aging and diabetes on atherosclerosis. The synergistic effect of aging combined with diabetes promotes a procoagulant, proliferative, and pro-inflammatory state inducing atherosclerosis with increased vasoconstriction and reduced vasodilatation. AGE, advanced glycation products.

system are themselves increasingly recognized as risk factors for atherosclerosis and CVD (Figure 7.1).

7.2.1 Aging effect

The effect of age on the vasculature is manifested by the fact that the risk of CVD increases with age. Aging is associated with structural and functional vascular changes.

Microscopically, the intima of the arterial wall becomes less smooth with increased deposition of lipid, calcium, and connective tissue. In the media there is increased deposition of elastic fibers and smooth muscle cells. Macroscopically, there is an increase in the arterial lumen size and arterial wall thickening, especially the intima. This leads to stiffening of the vascular wall and loss of compliance of the aorta and major arteries [3]. This loss of compliance plays a central pathophysiologic role in systolic hypertension in older people. The generalized stiffening of the arterial tree leads to increased systolic blood pressure, decreased diastolic blood pressure, and a widened pulse pressure. Increased pulse wave velocity is associated with increased adverse cardiovascular events and all-cause mortality [4]. Elastic recoil of the central arteries in diastole is important for coronary perfusion. Loss of this elasticity impairs coronary blood flow and may contribute to the development of CHD. Aging is also associated with endothelial dysfunction. The endothelium is a single layer of cells lining the blood vessels that plays a key role in regulating arterial function through synthesizing and releasing a balanced amount of biologically active molecules that modulate arterial vasodilatory and thrombolytic functions. Among the important molecules synthesized by the endothelial cell is nitric oxide (NO), which causes vasodilatation and protects the blood vessels from endogenous injury by mediating molecular signals that prevent platelet and leukocyte interaction with the vascular wall and inhibit vascular smooth muscle cell proliferation and migration [5]. With aging, alterations in the balance of these biological molecules occur with a shift towards a vasoconstrictor, procoagulant, proliferative, and proinflammatory state, leading to the development of atherosclerosis. Age-related endothelial dysfunction includes impaired endothelial-dependent vasodilatation due to reduced NO bioavailability and decreased vascular response to endothelial-released vasodilatory prostaglandins [6]. At the myocardium level, prolonged exposure to high systolic blood pressure leads to increased myocyte turnover with subsequent hypertrophy and interstitial fibrosis. This results in stiff non-compliant myocardium. The non-compliant myocardium leads to diastolic dysfunction and impaired early diastolic filling of the ventricles [7]. Left ventricular hypertrophy has been shown to be associated with increased risk of CVD [8]. This vascular aging precedes and predicts a higher risk for developing clinical disease. What is now referred to as vascular disease could be regarded as the vascular-aging/vascular-disease interaction [9]. This results in a steep increase in the prevalence and incidence of CHD by increasing age.

7.2.2 Diabetes effect

The mechanism of atherosclerosis in diabetes is multifactorial in origin, including endothelial dysfunction, hypercoagulability, and platelet dysfunction. In diabetes endothelin (vasoconstrictor and procoagulant) production increases and nitric oxide production decreases. This favors a procoagulant state and promotes vascular smooth muscle growth, causing an increased risk of cardiovascular events [10]. Hyperglycemia induces a series of cellular events that increase the production of reactive oxygen species such as superoxide anion that inactivate NO and produce oxygen-derived free radicals [11]. Hyperglycemia also accelerates atherosclerosis by triggering a non-enzymatic reaction between glucose and arterial wall proteins, resulting in the formation of advanced glycation end products (AGE) that are thought to be directly related to structural wall changes and endothelial cell dysfunction [12]. Circulating glucose molecules freely enter platelets, raising intracellular glucose concentration and leading to activation of protein kinase C, decreased platelet derived NO, and increased expression of the platelet aggregation mediator glycoprotein Ib [13]. The increased risk of CVD in diabetes is not fully explained by the traditional risk factors and there is some evidence to suggest that abnormalities of insulin-like growth factor 1 and one of its binding proteins, insulin-like growth factor binding protein 1, occur in insulin-resistant states and may be significant factors in the pathophysiology of CVD [14]. At the myocardium level, diabetes affects cardiac function through reduction of free fatty acids utilization as a cardiac energy substrate, impairs endothelial function, alters cellular metabolism, and induces autonomic neuropathy, resulting in systolic and diastolic dysfunction and changes in coronary blood flow [15]. Left ventricular mass increases with diabetes. In the Cardiovascular Health Study in a cohort of 5201 men and women ≥65 years of age, echocardiogarphically measured ventricular septal and left posterior wall thicknesses were greater in people with compared to those without diabetes, showing a significant linear trend with increased duration of diabetes ($p=0.025$ for ventricular septal thickness and $p=0.002$ for posterior wall thickness). Increased wall thickness of the ventricular septum or the left posterior wall was not associated with prevalent CHD in the cohort. After adjusting for body weight, blood pressure, heart rate, and prevalent coronary or cerebrovascular disease, diabetes remained an independent predictor of increased left ventricular mass among men and women (174.2 g in men with diabetes vs 169.8 g in normal men, 138.2 g in women with diabetes vs 134.0 g in normal women, $p=0.043$ for both sexes combined). This association between diabetes and left ventricular mass appears to be duration and severity dependent [16]. Diabetes also impairs cardiac diastolic function, leading to a myopathic state known as diabetic cardiomyopathy. This involves prolongation of contraction and relaxation as well as slowing in relaxation velocity [17]. Potential abnormalities underlying this cardiomyopathy include hyperglycemia, hyperinsulinemia, and alterations in cell membrane electrolyte channel functions [18]. Impaired left ventricular function occurs before clinical diabetes and affects individuals with impaired glucose tolerance [19]. This may make those with diabetes more prone to heart failure and other cardiovascular events independent of the traditional cardiovascular risk factors (Box 7.1).

Box 7.1 Aging and diabetes effect on the cardiovascular system.

Aging effect

- Increased arterial wall thickness and stiffness.
- Predisposition to systolic hypertension and wide pulse pressure.
- Loss of elastic recoil of aorta and impaired coronary filling.
- Hypertrophy and diminished compliance of the ventricles.

Diabetes effect

- Structural arterial wall changes and endothelial dysfunction.
- Predisposition to a procoagulant state.
- Increased ventricular mass.
- Diastolic dysfunction and diabetic cardiomyopathy.

7.3 Epidemiology of CHD

As the prevalence of type 2 diabetes is increasing rapidly due to aging of the population and the increased frequency of obesity, the prevalence of associated CVD is likely to increase [20]. The prevalence of CHD is around 80% of elderly Americans with type 2 diabetes [21]. The burden of CHD is also high in older people (≥65 years) with type 1 diabetes. The prevalence was

around 27.6% in a British study of 400 general practices in 2008. Older age (odds ratio (OR) 1.04, 95% confidence interval (CI) 1.02–1.07, $p=0.001$), longer duration of diabetes (OR 1.20, 95% CI 1.06–1.36, $p=0.003$), smoking (OR 1.41, 95% CI 1.06–1.87, $p=0.019$), and higher HbA1c (OR 1.16, 95% CI 1.05–1.30, $p=0.006$) were all shown to be significantly associated with the presence of macrovascular disease in the elderly type 1 diabetes population [22]. CVD is the most common cause of death in patients with diabetes, affecting around 65–80%, compared with only one-third of all deaths in the general population [23]. Silent or asymptomatic CHD is also highly prevalent among patients with diabetes. Autopsy studies have reported a prevalence of CHD in individuals with diabetes but without ante-mortem evidence of clinical CHD ranging from 50% to 75% [24]. Screening for CHD in patients with diabetes will not alter risk factor management because these patients are considered at high risk on the basis of diabetes alone [25]. However, screening may be useful in high-risk patients in whom revascularization therapy will be indicated. This is particularly important since CHD in older patients with diabetes may be asymptomatic or present atypically (e.g. shortness of breath instead of chest pain) compared to patients without diabetes [26]. The incidence of CHD is also higher in people with than in those without diabetes. In a prospective study of a cohort of older people (>65 years old) with diabetes followed up for 6 years after first being diagnosed as having diabetes, approximately 40% were diagnosed as having heart failure vs 20% for the control groups. Similarly, the rate of myocardial infarction was twice that in patients with compared to those without diabetes [27].

7.4 Cardiovascular risk

Diabetes confers at least a two-fold excess cardiovascular risk independently from other conventional risk factors. The Emerging Risk Factors Collaboration meta-analysis of 102 prospective studies showed an adjusted hazard ratio (HR) of 2.0 (95% CI 1.83–2.19) for CHD in people with compared to those without diabetes [28]. The cardiovascular risk increases further in relation to duration of diabetes, low estimated glomerular filtration rate (eGFR), and presence of proteinuria. The cardiovascular risk varies from a relatively low (two-fold) short-term risk in patients with newly diagnosed or short duration of uncomplicated diabetes to a higher risk (four- to five-fold) in patients with longer duration of diabetes, established CHD, low eGFR (<60 ml/min/11.73 m^2), and proteinuria [29]. Not only does diabetes increase the risk of CHD but adverse events associated with symptomatic CHD, such as cardiovascular death, myocardial infarction or recurrent ischemia, are also higher in patients with than in patients without diabetes, and the outcomes after coronary revascularization, such as increased rate of stent thrombosis and mortality after coronary artery bypass grafting, are worsened by the presence of diabetes [30]. Pre-diabetic conditions (impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT)) are also associated with a modest cardiovascular risk. The relative risk (RR) for CVD associated with IGT ranges from 0.97 to 1.30 and that associated with IFG ranges from 1.12 to 1.37 [31]. However, it is not clear whether the risk for developing CVD confined to people with pre-diabetes who will develop diabetes or whether the risk is still increased among people with pre-diabetes even if they never develop diabetes [31]. There is a sex-specific association between diabetes and incident CHD: women with diabetes have a more than 40% greater risk of developing CHD compared to men with diabetes (RR ratio 1.44, 95% CI 1.27 to 1.63) [32]. This difference is not explained by the traditional cardiovascular risk factors such as blood pressure and dyslipidemia but may be explained by the greater adverse influence of diabetes per se on adiposity, insulin resistance, blood pressure, lipids, endothelial dysfunction, and systemic inflammation in women compared with men [33]. It is suggested that women have to undergo more metabolic and vascular deterioration than men before developing diabetes [32]. Diabetes in older people confers a risk for cardiovascular mortality similar to that from established clinical CHD. Data from the Cardiovascular Health Study of 5784 participants (aged ≥65 years) showed that CHD mortality risk was similar between participants with CHD alone vs diabetes alone (HR 1.04, 95% CI 0.83–1.30) after multivariable adjustment for other CVD risk factors and subclinical atherosclerosis. The adjusted relative hazard for total mortality was lower among participants with CHD alone (HR 0.85, 95% CI 0.75–0.96) compared with those who had diabetes alone. This elevated total mortality rate among older adults with diabetes can be partially explained by the

increased prevalence of inflammation and renal dysfunction in diabetes [34]. It has also been shown that individuals who develop diabetes after the age of 60 and have a short duration of diabetes (average of 1.9 years) have a CHD risk around half that of men of similar age who develop diabetes before 60 (average duration around 16.7 years), with only the latter group having a similar risk to those with previous myocardial infarction and no diabetes. In other words, duration of diabetes matters to CHD risk and, typically, a diabetes duration of 8 years or more is needed to reach a CHD risk equivalent state [35]. A comparison of crude CHD mortality rates in individuals with diabetes alone (2.0%), CHD alone (2.5%) or both (5.4%) suggests that the mortality rate in participants who have both conditions is greater than additive. Therefore, the public health burden of both prevalent conditions is substantial in older people and suggests that intensely treating cardiovascular risk factors in the elderly with diabetes is important [34] (Box 7.2).

Box 7.2 Cardiovascular risk in older people with diabetes.

- Diabetes increases cardiovascular risk by tow- to four-fold.
- Pre-diabetes state (IFG and IGT) modestly increases cardiovascular risk.
- Duration of diabetes, established CHD, low eGFR (<60 ml/min per 1.73 m^2) and proteinuria are determinants of increased cardiovascular risk.
- Diabetes worsens outcomes associated with CHD, such as increased mortality, myocardial infarction, and stent thrombosis after revascularization.
- There is sex-specific association between diabetes and incident CHD, with women having >40% greater risk compared with men.
- Diabetes in older people confers a risk equivalent to myocardial infarction.
- Duration of diabetes (>8 years) is the main determinant of myocardial infarction risk equivalence.
- The cardiovascular risk associated with diabetes and established CHD is more than additive.
- Absolute risk reduction is higher and more cost-effective in patients with compared to those without diabetes.

IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate.

7.5 Prevention and management of CHD

CVD remains the main cause of mortality, affecting about 50–75% of all deaths in patients with diabetes [36]. Prevention of CHD is most important as individuals with diabetes continue to have worse prognosis following cardiac events. For example, mortality after per cutaneous coronary artery intervention for myocardial infarction in patients with diabetes is significantly higher than in those without diabetes (7.4% vs 3.8% at 1 month and 13.9% vs 6.5% at 12 months, respectively) [37]. Mortality after coronary artery bypass grafting in individuals with diabetes is more than 50% higher at 1, 5, and 10 years postoperatively compared with those without diabetes [38]. Similarly, drug-eluting stents do not improve clinical outcome in individuals with diabetes [39]. Older patients with diabetes have a higher baseline cardiovascular risk and therefore are likely to benefit more from risk reduction than younger patients without diabetes. Prevention and management of cardiovascular risk factors should include both lifestyle modification and pharmacological interventions. The major cardiovascular risk factors include smoking, hyperglycemia, hypertension, dyslipidemia, visceral obesity, insulin resistance and hyperinsulinemia. Hyperglycemia, therefore, should not be treated in isolation but a holistic view of the collective cardiovascular risk should be adopted and constitutes a comprehensive plan of intervention and risk reduction (Box 7.3).

7.5.1 Lifestyle modification

Lifestyle modification includes changes in diet, weight reduction, smoking cessation, and regular exercise to reduce visceral obesity and improve insulin sensitivity. Smoking cessation may be the single most effective means of reducing mortality in high-risk populations [40]. Smoking induces vasoconstriction and toxic effects on the endothelium. One year of smoking cessation results in a reduction by half or more of the excess risk associated with current smoking. However, many years of cessation are needed to reduce the risk of an ex-smoker to that of a non-smoker. A diet that is high in fiber and potassium, and low in saturated fat and refined carbohydrates and salt improves the lipid profile and significantly lowers blood pressure [41]. The achievement of ideal body weight through diet changes and exercise

Box 7.3 Prevention and management of CHD in older people with diabetes.

Life style modification

- Smoking cessation, balanced diet, weight loss, and regular exercise.
- Smoking cessation improves endothelial function.
- Weight loss, balanced diet, and regular exercise will improve the metabolic profile of lipids, glycemia, blood pressure, and insulin sensitivity.

Metabolic syndrome

- The prevalence of metabolic syndrome increases with age and diabetes.
- Metabolic syndrome increases risk of atherosclerosis through the synergistic effects of its components.
- Much of the adverse effects associated with metabolic syndrome may be explained by the presence of insulin resistance.

Dyslipidemia

- The absolute benefit of statin therapy in older patients with diabetes is substantial, and all patients should be offered statins unless specifically contraindicated or life expectancy is limited by frailty and co-morbidities.
- The routine use of fibrate or niacin in addition to statin is not recommended.

Hypertension

- Prevalence of hypertension increases with diabetes.
- Cardiovascular risk reduction is more beneficial with blood pressure regulation than blood glucose control.
- The benefit per mmHg blood pressure reduction is greater in patients with compared to those without diabetes.
- Thiazide diuretics, ARBs, ACE inhibitors, and CCBs are reasonable first-choice antihypertensive agents.
- A target blood pressure around 140 mmHg systolic is recommended in older patients with diabetes and a more relaxed target in very old and frail patients is reasonable.

Hyperglycemia

- Hyperglycemia is associated with increased risk of CVD although the relationship between tight glycemic control and reduction of CVD is controversial.
- Tight glycemic control may have benefit in those newly diagnosed with diabetes who have low prevalence of cardiovascular risk factors.
- In those with a longer history of diabetes and established CVD, the benefit is less clear.

Aspirin therapy

- Diabetes increases platelets adhesion and aggregation.
- Aspirin therapy should be considered selectively in older patients with diabetes and high cardiovascular risk but after assessment of their bleeding risk.

CHD, coronary heart disease; ARBs, angiotensin receptor blockers; ACE, angiotensin converting enzyme; CCBs, calcium channel blockers; CVD, cardiovascular disease.

will reduce the overall cardiovascular risk and will have a favorable effect on the metabolic profile of lipids, glycemia, and blood pressure. In the Diabetes Prevention Program, lifestyle intervention including modest weight reduction, a healthy low-fat diet, and regular exercise reduced the development of diabetes in older people and this beneficial effect persisted for up to 10 years after the end of the study [42]. Weight loss can be maintained for a long period (up to 30 months) in obese older people randomized to dietary interventions, exercise or both [43]. Lifestyle interventions improve insulin sensitivity and the metabolic risk factors for CHD [44]. Additional benefits of exercise for older people may include increased muscle strength and improved

walking balance. The Look AHEAD (Action for Health in Diabetes) study in middle-aged and older people with type 2 diabetes showed that weight loss and improved fitness lowered the risk for loss of mobility [45], therefore walking and resistance training are suitable for older people and should be encouraged.

7.5.2 Metabolic syndrome

Cardiovascular risk factors rarely occur in isolation but rather tend to cluster in what is known as metabolic syndrome. This is characterized by a group of risk factors including visceral obesity, dyslipidemia (low high-density lipoprotein cholesterol (HDL), high triglycerides (TG) and elevated apolipoprotein B, and small dense low-density lipoprotein (LDL)), hypertension, and impaired glucose/insulin homeostasis (insulin resistance, hyperinsulinemia and glucose intolerance) [46]. The prevalence of metabolic syndrome increases with age. Prevalence in a cohort of 2175 older people above the age of 65 years from the Cardiovascular Health Study was 21–28% [47]. In the Three City Study of 5585 French non-institutionalized older people (65–85 years old) without diabetes, prevalence of metabolic syndrome was 12.1% [48]. In a Norwegian study, the prevalence of metabolic syndrome increased from 11.0% in the 20–29-year-old group to 47.2% in the 80–89-year-old group in men, and from 9.2% to 64.4% for women in the corresponding age groups [49]. However, the magnitude of metabolic syndrome in older people with diabetes is higher. The prevalence was 64.9% and 87.1% in men and women with diabetes, respectively, and 25.9% and 55.2% in men and women without diabetes in a population-based study of a sample of 5632 Caucasian cohort (65–84 years old) [50]. The prevalence of metabolic syndrome also increases with increasing glucose intolerance. In the Third National Health and Nutrition Examination survey (NHANES III) of the US population ≥50 years of age, there was a stepwise increase in the prevalence of metabolic syndrome with worsening glucose tolerance from almost 26% in those with normal fasting glucose rising to 86% in those with diabetes [51]. The metabolic syndrome is increasingly recognized as a risk factor for CVD [52]. It was associated with ischemic electrocardiographic changes in 2274 elderly subjects enrolled in the Rancho Bernardo cross-sectional study [53]. Metabolic syndrome may have adverse effects on the structural and functional properties of the arteries, such as increasing arterial wall stiffness and thickness through a synergistic effect of the clustering of its components [54]. In a prospective study of 888 subjects aged 40–79 years, metabolic syndrome conferred a significantly increased risk for developing new carotid plaques (HR 1.5), new carotid stenosis (2.5), and new coronary events (2.3) [55]. However, in another prospective study of 1025 elderly subjects aged between 65 and 74 years, metabolic syndrome was shown to be a marker of CVD but not above and beyond the risk associated with its individual components [56]. In an analysis of the outcome of another two prospective studies in an elderly population above the age of 60 years, metabolic syndrome and its components were associated with type 2 diabetes but had modest association with cardiovascular risk [57]. Therefore metabolic syndrome in the elderly may not enhance risk prediction and the criteria of metabolic syndrome may not offer more than the sum of its components. Also, in the Framingham Heart Study of 2910 participants without diabetes or a history of CHD, incident CHD risk associated with dyslipidemia, defined as high TG and low HDL cholesterol, was significantly increased only in the presence of insulin resistance. Compared with a reference group without insulin resistance and with a higher than median HDL or lower than median TG, the hazard ratio for incident events was significant only with insulin resistance and a lower HDL (HR 2.83, $p<0.001$) or TG (HR 2.50, $p<0.001$) adjusted for major CHD risk factors including waist circumference. Dyslipidemia is associated with obesity and other features that define metabolic syndrome and it is possible that much of the CVD that is associated with metabolic syndrome may be explained by the presence of insulin resistance [58].

7.5.3 Dyslipidemia

High cholesterol level is associated with increased cardiovascular events and mortality. There is a positive relationship between serum cholesterol level and cardiovascular risk. Statins are effective in lowering cholesterol and reducing the risk of cardiovascular events. Their efficacy has been demonstrated in clinical trials on high-risk individuals. There are no large clinical trials of lipid-lowering interventions specifically in older people with diabetes. The benefits of statins in older people with diabetes have been extrapolated from trials of

adults without diabetes and trials of adults with and without diabetes. The evidence for cholesterol lowering is evident for individuals up to the age of 80 years. For those aged above 80 years, there is some evidence of benefit from observational studies [59–61]. No mortality benefit was found for those aged above 80 years who received a statin, whereas those aged 65–79 years had a significant 11% reduction in mortality. There was evidence, however, of a trend toward benefit in those aged 80–85 years versus those aged above 85 years [61]. Although the positive association between total and LDL cholesterol and cardiovascular risk becomes attenuated with advancing age [62], the Cholesterol Treatment Trialists Collaborators (CTTC) systematic prospective meta-analysis, which reported data from 14 randomized clinical trials, showed that individuals aged >65 years ($n=6446$) had 19% reduction in the risk of major cardiovascular events, similar to the 22% reduction in the risk experienced by those aged <65 years ($n=7902$) [63]. Statins reduce the proportional risk as effectively in older as in younger people, but limited data are available for elderly patients with type 2 diabetes. In the CTTC meta-analysis, which included 18,686 patients with diabetes out of a total of 90,056 participants, there was a 21% reduction (95% CI 19–23) in major vascular events per 1 mmol/l reduction in LDL cholesterol and no difference in treatment effect between patients with diabetes and those without diabetes [63]. The heart protection study included a total of 20,536 patients between the ages of 40 and 80 years. There were 5806 (28%) older patients above the age of 70, and a total of 5963 (29%) patients with diabetes. The reduction in cardiovascular events obtaining by simvastatin 40 mg daily was 25% after 5 years of follow-up in all subgroups irrespective of cholesterol levels at the start of treatment. Although the RR reduction was similar in all subgroups, the absolute benefit depends on the individual's baseline risk, which is higher in people with diabetes [64, 65]. In a meta-analysis of 12 studies to evaluate the clinical benefit of lipid lowering in patients with and without diabetes mellitus, the risk reduction of major coronary events was 21% (95% CI 11–30%, $p<0.0001$) and 23% (95% CI 12–33%, $p=0.0003$), respectively. When results were adjusted for baseline risk, the benefit was more in patients with diabetes [66]. The post-hoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS) compared the primary prevention efficacy and safety of atorvastatin in 1129 patients aged 65–75 years at randomization with 1709 younger patients without elevated LDL cholesterol concentrations. Treatment with 10 mg/day atorvastatin resulted in a 38% reduction in RR (95% CI –58 to –8, $p=0.017$) of first major cardiovascular event in older patients and a 37% reduction (95% CI –57 to–7, $p=0.019$) in younger patients. The corresponding absolute risk reductions were 3.9 and 2.7%, respectively (difference 1.2%, 95% CI –2.8 to 5.3, $p=0.546$), and the numbers needed to treat (NNT) for 4 years to avoid one event were 21 and 33, respectively. The higher absolute risk reduction and lower NNT in the elderly reflect their higher baseline risk. All-cause mortality was reduced non-significantly by 22% (95% CI –49 to 18, $p=0.245$) and 37% (95% CI –64 to 9, $p=0.98$), respectively. The reduction in total cholesterol, LDL cholesterol, and TG as well as safety profile were similar in both groups. This suggests that the absolute and relative benefits of statin therapy in older patients with type 2 diabetes are substantial and all older patients with diabetes warrant treatment unless specifically contraindicated [67]. The use of fenofibrate in patients with diabetes is not yet clear. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial, which included 5518 patients, all on simvastatin therapy, who were randomized to fenofibrate or placebo, there was no difference in the rate of fatal or non-fatal cardiovascular events, stroke or death after 5 years of follow-up despite significantly lower TG and higher HDL levels in the fenofibrate arm, therefore the routine use of a fibrate in addition to a statin therapy is not recommended [68]. Similarly, niacin treatment in patients with established vascular disease on a statin with low HDL and high TG significantly increased HDL, lowered TG, and lowered LDL levels but failed to reduce mortality from CHD or cardiovascular events [69]. It appears from the above that statins should be prescribed for all older people with diabetes who have reasonable life expectancy. Chronological age in and of itself should not exclude patients from receiving therapy but the functional or biological age of the patient and the impact of long-term drug therapy on safety and quality of life should be considered. Given the larger reduction in event rates in older patients, treatment would also be expected to be more cost-effective in older than in younger patients [70]. Moderate-dose statins appear to

be well tolerated in elderly people participating in clinical trials, although the risk of serious muscle adverse effects may be slightly higher. Higher doses of statins should be used with caution in frail elderly patients, who may be more susceptible to drug-related myopathy and other side effects as statin toxicity is dose related.

7.5.4 Hypertension

Hypertension is commonly associated with type 2 diabetes and adds to the increased risk for CVD, therefore screening and treating hypertension in older patients with diabetes is essential:

7.5.4.1 Risk reduction

Hypertension affects up to 60% of patients with type 2 diabetes and this prevalence is about three times that of patients without diabetes [71]. Increasing age, obesity, and the onset of renal disease are the contributing factors to increasing prevalence of hypertension in type 2 diabetes. The development of diabetes is also about twice as likely as in people with hypertension compared to normotensive individuals, suggesting the common coexistence of these two chronic diseases [72]. Hypertension markedly increases the risk for CVD in patients with type 2 diabetes compared to those without diabetes [71]. Blood pressure control markedly reduces CVD as well as the development of end-stage renal disease in people with type 2 diabetes mellitus [73]. This risk reduction was even more impressive than the tight blood glucose control in the United Kingdom Prospective Diabetes Study (UKPDS). The benefits of blood pressure reduction to 144/82 mmHg in the tight control group vs 154/87 mmHg in the usual care group dramatically outweighed those of intensive glucose control [74]. Reduction of diastolic blood pressure to less than 80 mmHg reduced CVD events by 51% in comparison to diastolic blood pressure of 90 mmHg in participants with diabetes in the Hypertension Optimal Treatment (HOT) study [75]. In contrast, HOT study participants without diabetes received no benefit from this further diastolic blood pressure reduction. Reduction of the systolic pressures from 175 to 153 mmHg resulted in a significant reduction in CVD events in the Systolic Hypertension in Europe (Syst-Eur) trial [76]. Patients with diabetes gained more benefit from aggressive blood pressure lowering than patients without diabetes. In that trial, although systolic blood pressure was reduced by a comparable amount in each group (22.0 mmHg) the risk reduction in mortality from CVD was 13% in participants without diabetes compared to 76% for participants with diabetes. This has also been shown in the Systolic Hypertension in the Elderly Program (SHEP) study, where elderly people with type 2 diabetes derived more benefit from aggressive systolic blood pressure lowering in reducing the risk of CVD than did those without diabetes [77]. From the above, it appears that the benefit per mmHg blood pressure reduction is greater in patients with compared to those without diabetes.

7.5.4.2 Antihypertensive medication

Angiotensin converting enzyme (ACE) inhibitors may have a role in reducing cardiovascular risk in older patients with diabetes. The elderly Heart Outcomes Prevention Evaluation (HOPE) trial included 2755 older patient ≥ 70 years of age with vascular disease or diabetes and at least one additional cardiovascular risk factor and without heart failure. They were randomized to ramipril 10 mg daily or placebo for 4.5 years of follow-up. Those assigned to ramipril had fewer major vascular events (18.6% vs 24.0%, HR = 0.75, $p = 0.0006$), cardiovascular deaths (9.3% vs 13.0%, HR = 0.71, $p = 0.003$), myocardial infarctions (12.0% vs 15.6%, HR = 0.75, $p = 0.006$), and strokes (5.4% vs 7.7%, HR = 0.69, $p = 0.013$) compared to those assigned to placebo. The risk reduction and safety profile of ramipril were similar to those observed in younger people aged <70 years. Importantly, due to the high baseline cardiovascular risk in older patients, the absolute risk reductions attained with ramipril were higher in this age group. For example, the absolute risk reduction for the primary endpoint was 5.4% in patients ≥70 years and 3% for those <70 years, so for elderly patients the NNT to prevent one major cardiovascular event over 4.5 years was 18 compared to 33 for younger patients [78]. β-blockers are associated with an increased risk for new onset diabetes mellitus with no benefit for the end point of death or myocardial infarction and with a 15% increased risk for stroke compared with other agents. A meta-analysis of 12 studies evaluating 94,492 patients taking β-blockers as first-line therapy for hypertension with data on new onset diabetes and follow-up for more than 1 year showed that β-blocker therapy resulted in a 22% increased risk for new onset diabetes (RR 1.22, 95% CI 1.12–1.33) compared with non-diuretic antihypertensive agents.

A higher baseline fasting blood glucose level was a significant predictor of new onset diabetes (OR 1.01, 95% CI 1.00–1.02, $p=0.004$). On the other hand, calcium channel blockers (CCBs) and ACE inhibitors or angiotensin II receptor blockers (ARBs) resulted in 21% and 23% reductions, respectively, in the risk for new onset diabetes compared with β-blockers [79]. Also in comparison with other antihypertensive agents, the antihypertensive efficacy of β-blockers was inferior. In this analysis, however, diuretics resulted in an increased risk of new onset diabetes compared with β-blockers, but their blood-pressure-lowering efficacy was more superior. In the UKPDS, although the β-blocker atenolol efficacy was similar to the ACE inhibitor captopril, patients taking atenolol gained more weight and required more frequent addition of new glucose-lowering agents than those taking captopril [74]. A meta-analysis showed that the association of an antihypertensive class of drug on incident diabetes was lowest for ARBs, ACE inhibitors followed by CCBs, β-blockers, and diuretics in that order [80]. The ARBs similar to ACE inhibitors also have a beneficial effect in reducing renal end points and cardiovascular events [81–83]. The Losartan Intervention for Endpoint Reduction (LIFE) study randomly assigned patients with hypertension and signs of left ventricular hypertrophy on electrocardiography to an ARB (losartan) or a β-blocker (atenolol). In a subgroup analysis of 1195 patients with diabetes, the losartan group had a substantially lower risk for cardiovascular end points and total mortality [84]. In summary, the risk reduction with hypertension control in patients with diabetes is substantially greater than that in people without diabetes who have similar blood pressure levels. Most patients will require more than one antihypertensive agent. Thiazide diuretics, ARBs, ACE inhibitors, and CCBs are reasonable first-choice agents, although higher doses of diuretics could worsen blood glucose and lipid levels. Addition of antihypertensive agents other than the above may be necessary to achieve blood pressure targets.

7.5.4.3 Blood pressure targets

A target blood pressure around 140 mmHg systolic is reasonable in older patients with diabetes. It has been shown that blood pressure control to maintain systolic BP between 130 and 140 mmHg is associated with reduction of adverse cardiovascular outcomes compared to uncontrolled systolic BP >140 mmHg among hypertensive patients (age ≥50 years) with diabetes and CHD after 3 years of follow-up. The International Verapamil SR-Trandolapril Study (INVEST) concluded that controlling systolic blood pressure <130 mmHg was not associated with better cardiovascular outcomes than the usual control of 140–130 mmHg in individuals aged 55 and older, mean (SD) age 66 (6) and it was associated with slightly increased risk of mortality (11.0% in the tight vs 10.2% in the usual control groups, respectively (adjusted HR 1.20, 95% CI 0.99–1.45, $p=0.06$) [85]. In very old patients (>80 years) targets may be even more relaxed. The Hypertension in the Very Elderly Trial (HYVET), which included older people ≥80 years of age with sustained systolic blood pressure >180 mmHg, 7% of whom had diabetes, showed a significant 33.7% (HR 0.66, 95% CI 0.53–0.82, $p<0.001$) reduction in cardiovascular events (death from cardiovascular causes or stroke, myocardial infarction or heart failure) with blood pressure control (target BP 150/80 mmHg). However, it is important to realize that the individuals included in the HYVET were generally healthier than those in the general population, with a low baseline rate of known CVD (11.5%), myocardial infarction (3.1%) or heart failure (2.9%) therefore the results may not apply to all older persons, especially those with multiple co-morbidities or living in care homes [86]. Tight blood pressure control should be generally avoided in older people with diabetes. The ACCORD Blood Pressure study compared intensive blood pressure treatment (target of <120 mmHg systolic blood pressure) with standard treatment with a goal of 140 mmHg in middle-aged and older adults (40–79 years) with diabetes and a high risk of CVD [87]. The study did not find statistically significant reductions in the primary outcomes (myocardial infarction or all-cause mortality) but found modestly statistically significant fewer secondary outcome events (stroke) in the intensive treatment arm but with increased rates of serious adverse events. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) also had similar conclusions for older individuals, mean (SD) age 66 (7) 57% of whom were ≥65 years old [88]. Two meta-analyses of older people with diabetes did not show benefits for myocardial infarction or mortality over a blood pressure of less than 140 mmHg [89, 90].

7.5.5 Hyperglycemia

The relationship between hyperglycemia and cardiovascular disease is established. A meta-analysis of prospective cohort studies showed an 18% (pooled RR 1.18, 95% CI 1.10–1.26) and 15% (RR 1.15, CI 0.92–1.43) greater relative risk of CVD per 1% increase in HbA1c in type 2 and type 1 diabetes, respectively [91]. Even studies in individuals without diabetes have shown an association between fasting blood glucose level and CVD [92]. However, so far there is no convincing evidence that reducing blood glucose to near normal levels results in lower cardiovascular events. Early data from the UKPDS, which included 5102 newly diagnosed patients with diabetes, mean (SD) age 54 (8), showed equivocal results with a non-significant ($p=0.052$) 16% reduction in myocardial infarction with tight glycemic control but significant reduction by 39% ($p=0.01$) in the metformin group, which included only 342 obese patients [93]. This was followed by data from three large prospective randomized trials which failed to show macrovascular benefits of intensive blood glucose reduction. The ACCORD [94], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [95], and Veterans Affairs Diabetes Trial (VADT) [96] studies included 10,251 (mean (SD) age 62.2 (6.8), 11,140, mean (SD) age 66 (6) and 1791, mean (SD) age 60.5 (9), respectively) type 2 diabetes patients with coexisting risk factors and history of cardiovascular complications. The ACCORD study was prematurely discontinued after 3.5 years of follow-up due to excess mortality in the intensive therapy arm. The ADVANCE trial demonstrated a 10% reduction in the composite of micro- and macrovascular events (HR 0.90, 95% CI 0.82–0.98, $p=0.01$) over a 5-year follow-up but it did not remain significant after adjustment for reduction in nephropathy. The VADT study showed no significant reduction in the cardiovascular events (HR 0.88, 95% CI 0.75–1.05, $p=0.14$). The intensive therapy arms across the three studies reported higher incidence of weight gain and hypoglycemia requiring medical assistance. However, in the UKPDS follow-up study risk reduction of myocardial infarction emerged after 10 years (HR 0.85; 95% CI 0.74–0.97, $p=0.01$). In the metformin group, significant risk reduction of myocardial infarction persisted (HR 0.67, 95% CI 0.51–0.89, $p=0.005$) [97]. It is worth noting that the UKPDS population was relatively young and healthy. The study included only patients with newly diagnosed diabetes and excluded those with significant CVD (previous myocardial infarction, current angina or heart failure). In contrast, participants in the three more recent studies were older, had longer duration of diabetes, high use of insulin (among 35–50% of subjects), and a third (32–40%) already had pre-existing heart disease, suggesting that their CVD was already established before intervention, minimizing the benefit of tight glucose control. It is possible that the multiple interventions with blood pressure control, statins, and antiplatelet therapy in these three trials reduced the rate of endpoint events, reducing the power of these studies and minimizing the effect of tight glucose control on outcome. The increased mortality in the ACCORD study was not clearly explained. In the intensive therapy group, a median HbA1c of 6.4% was rapidly achieved after only 4 months of randomization. The increased mortality could be related to multiple factors, including the speed of glucose lowering and the treatment used to achieve such a level. Of note, after about 3 years, a non-significant reduction in the primary outcome (non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular events) started to emerge in the intensive therapy group. Moreover, the results of this study were not consistent, as there was a significant reduction in non-fatal myocardial infarctions in the intensive (3.6% vs 4.6%, $p=0.004$) compared with the standard treatment group. A meta-analysis of these recent trials showed that a reduction of HbA1c of 0.9% resulted in a 17% reduction in non-fatal myocardial infarction (OR 0.83, 95% CI 0.75–0.93), and 15% (OR 0.85, 95% CI 0.77–0.93) in combined fatal and non-fatal myocardial infarction but did not increase mortality (OR 1.02, 95% CI 0.87–1.19) [98]. Similar results have also suggested that vascular risk can be reduced with intensive glycemic control in patients with diabetes but without established macrovascular disease [99]. In a retrospective subgroup analysis of the ACCORD study assessing the impact of intensive glucose control in older (≥65 years) versus younger (<65 years) people, the intensive glucose control resulted in a higher incidence of CV mortality in the younger but not the older participants, indicating that advanced age per se was not related to increased risk. However, older participants in the ACCORD trial were community dwelling ambulatory patients and therefore these results cannot be generalized to more frail older patients [100]. The summary of these trials suggests that tight glycemic

Table 7.1 Summary of recent diabetes studies [94–97].

	ACCORD	ADVANCE	VADT	UKPDS follow up
Number of patients	10,251	11,140	1,791	3,277
Mean (SD) age (years)	62.2 (6.8)	66 (6)	60.5 (9)	62 (8)
Target HbA1c	<6%	≤6.5%	To reduce HbA1c by 1.5%	No target specified
Duration of diabetes on start of study (years)	10.0	8.0	11.5	Newly diagnosed on start of intervention study
History of macrovascular disease	35%	32%	40%	Patients with significant CVD were excluded
Cardiovascular outcome	Harmful effect	No benefit	No benefit	Beneficial effect

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; UKPDS, UK Prospective Diabetes Study; CVD, cardiovascular disease.

control will reduce cardiovascular complications in those newly diagnosed with diabetes, relatively younger patients, and those with low prevalence of cardiovascular risk factors, and that risk reduction will take some time to emerge. In older patients with a longer history of diabetes and established CVD, the cardiovascular benefits of tight glycemic control are less clear (Table 7.1).

7.5.6 Hypercoagulability and aspirin therapy

A procoagulant state has been shown in individuals with diabetes [101]. Platelet aggregation and adhesion are increased in diabetes [102]. Diabetes increases intrinsic platelet activation and decreases endogenous inhibitors of platelet activity [13]. These changes are likely due to the chronic inflammatory state induced by diabetes. Aspirin use in secondary prevention is established as it has been shown to be effective in reducing cardiovascular morbidity and mortality in patients with a history of CVD [103]. The evidence for aspirin use in primary cardiovascular risk prevention is still conflicting. A meta-analysis of aspirin treatment in patients with diabetes in large primary prevention studies demonstrated a trend towards a 10% reduction in cardiovascular events [104]. It appears that the presence of diabetes per se does not justify aspirin use. However, most older patients with diabetes will have a high burden of cardiovascular risk and are likely to benefit from aspirin therapy. Aspirin use should therefore be considered selectively in older patients with diabetes and high cardiovascular risk but after assessment of their bleeding risk [105].

7.5.7 Multifactorial intervention

Hyperglycemia should not be treated in isolation but collective cardiovascular risk should be assessed for a multi-intervention risk reduction. The comprehensive plan should start with lifestyle modifications in addition to cardiovascular risk factors management. In a randomized controlled study of patients with type 2 diabetes comparing structured multifactorial intervention, including behavior modification, aspirin use, and tight targets for blood pressure, glucose and lipids, the risk of CVD was reduced by 0.47 (95% CI 0.24–0.73) in the intervention group compared to a conventionally managed group after 8 years of follow-up [106]. The reduction in the cardiovascular mortality was sustained in the multifactorial intervention group (HR 0.43, 95% CI 0.19–0.67, $p<0.001$) after a total of 13.3 years of follow-up [107]. It appeared from the multifactorial interventional study that the use of statins and antihypertensive medications might have had the largest effect in reducing cardiovascular events, with hypoglycemic agents and aspirin the next most important interventions [108]. This comprehensive approach is still suboptimal in older people with diabetes as out of a total of 48,505 older patients (>66 years old) only 9912 (20.4%) were shown to use a comprehensive intervention of antihypertensive, lipid-lowering, and antiplatelet drugs in the year following oral hypoglycemic medications initiation [108].

7.5.8 Reverse metabolism

Older people with type 2 diabetes are heterogeneous individuals with varying degrees of co-morbidity and functional level. In frail older people the power of traditional cardiovascular risk factors such as hypertension, dyslipidemia and hyperglycemia to predict the risk of CVD seems to diminish with age, describing a paradoxical relationship [109]. The more commonly proposed explanations include the association of low body weight and low cholesterol with increased protein energy malnutrition and an increased inflammation associated with frailty [110]. In a study of 331 very old patients, mean (SD) age 85 (7) years, low body mass index, low blood pressure, low total and HDL cholesterol, and high insulin sensitivity predicted total mortality indicating a "reverse metabolism" that is probably attributable to malnutrition and/or chronic disorders, which have a negative impact on survival [111]. Low albumin (a marker of malnutrition) and high C-reactive protein (a marker of inflammation) were associated with these cardiometabolic factors, limiting their prognostic value in predicting cardiovascular risk in older people [111]. It is important to recognize that many older patients with diabetes are frail and at greater risk of developing common geriatric syndromes such as depression, cognitive impairment, physical dysfunction, urinary incontinence, and injurious falls. The diabetes guidelines are largely disease specific, age neutral, and driven by numerical surrogates such as HbA1c and blood pressure but do not necessarily consider outcomes relevant to older people such as physical function, disability or quality of life [112]. Importantly, indiscriminate application of these guidelines may lead to overtreatment and polypharmacy, with potential harm in this age group. Frail older people with diabetes are more likely to experience adverse effects to medications, therefore a gradual decrease in blood pressure is an essential strategy in treating hypertension to avoid symptoms of hypotension such as light headedness, dizziness, and subsequent falls. Avoidance of hypoglycemia is especially important in those with impaired kidney function as impaired renal clearance of insulin and hypoglycemic medications predispose them to hypoglycemia [113]. The expected benefit of glycemic control also declines as the levels of morbidity and functional impairment increase, thus functional status and level of co-morbidity are important factors in assessing their risk [114].

7.6 Conclusion

Aging and diabetes have a significant impact on the cardiovascular system, increasing the risk of developing CHD in older people with diabetes. The size of the problem is likely to expand as both the aging population and the incidence of diabetes are increasing. The combination of both diabetes and old age puts older people with diabetes at the highest baseline risk for CVD. Older people with diabetes therefore stand to gain the most benefit of cardiovascular risk reduction. Multifactorial intervention and a comprehensive approach are vital to management of diabetes in old age. Although most of the clinical trials have excluded older people or included only a few, there is now enough evidence to suggest that aggressive treatment of risk factors in this age group is beneficial and cost-effective. Many older people with diabetes may not achieve recommended targets for risk factor reduction for various reasons, such as multiple co-morbidities, polypharmacy, and intolerance of higher doses or multiple medications. However, any reduction in these risk factors is beneficial. Older people form a highly heterogeneous population ranging from a fit person living in the community to a frail individual with multiple co-morbidities living in a care home Some may therefore not be suitable for aggressive risk reduction and quality of life may on the whole be better with relaxed targets; these should form part of a patient-centered plan in the care of frail elderly people with diabetes.

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CHAPTER 8

Chronic kidney disease related to diabetes in older patients

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KEY MESSAGES

- Over a third of people with diabetes aged over 65 have different stages of chronic kidney disease, identified by reduced glomerular filtration rate (GFR), altered albuminuria or both.
- The current high percentage of diabetic patients presenting with reduced GFR with normal albuminuria could in part be a result of the systematic renin-angiotensin-aldosterone system (RAAS).
- The damage to the glomerulus and tubule-interstitium as well as macro- and microvascular involvement are caused by the confluence of metabolic and hemodynamic alterations, poor lifestyle, hormonal (particularly RAAS) influences, vitamin D deficiency, sympathetic/parasympathetic imbalance, and endothelins, along with genetic predisposition and natural aging.
- Following international guidelines, glycemic and blood pressure (BP) goals should be established at HbA1c levels between 7.0% and 8.5%, and BP between 140 and 150 systolic and <90 mmHg diastolic, according to the patient's clinical and functional status.
- Attention must be paid to the frequent reduction in lean body mass, risk of hypoglycemia, and degree of vascular injury.
- Medication should prioritize RAAS blockade and statins, adjusting dosage to GFR and avoiding unnecessary medications.

8.1 Introduction

The prevalence of chronic kidney disease (CKD) has grown significantly, affecting 35% of elderly patients over 65 years of age [1–4]. Most CKD in elderly patients is caused by type 2 diabetes mellitus, which together with hypertension and ischemic renal phenomena are responsible for the CKD world epidemic. It is important to note that aging in itself is associated with a progressive decline of renal functional reserve (RFR) [5], which favors CKD. In clinically healthy individuals aged 75, 30% of the glomeruli are obsolete due to glomerular sclerosis [6].

The progressive development of glomerulosclerosis and tubulointerstitial fibrosis is a well-known phenomenon that occurs in aging mammalian kidneys [7, 8], and it is also known that this natural process can be accelerated experimentally through the induction of diabetes mellitus, or through the reduction of renal mass by unilateral nephrectomy as well as by arterial hypertension [9–11]. Similar events can be described in human beings.

In diabetic kidney disease (DKD), and particularly in type 2 diabetes mellitus, the above structural changes are evidenced through two main renal clinical manifestations: (1) urinary protein loss (especially albumin), which indicates lesion of the glomerular structure, and (2) the progressive decline of renal function as assessed by calculating the glomerular filtration rate (GFR). Often both renal clinical alterations are present at the same time, although they do not necessarily evolve simultaneously and sometimes they do so in opposite

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directions or without a defined pattern. Differences between the degree of albuminuria and the GFR occur at different stages and clinical conditions of the disease. These variations are usually influenced by the degree of metabolic control as well as other factors such as dyslipidemia and the use of different drugs, but the strongest influences seem to be sodium chloride consumption and blood pressure (BP) levels.

The chronic nephropathy associated with diabetes mellitus is often called diabetic nephropathy, although it is well known that not all the changes are a consequence of the metabolic disorder. Diabetic nephropathy shows alterations in the normal histological structure of the kidney, mainly thickening of the glomerular basement membrane, expansion of the mesangium, damage at the podocyte level, and glomerular sclerosis. These are accompanied by alterations in: the tubulointerstitial structure and in the vast network of extrarenal and intraparenchymatose vessels, including alterations in the capillary bed. Most of these changes occur in type 1 and type 2 diabetes mellitus, as well as in other secondary forms of diabetes, depending on the duration of the disease and the persistence of hyperglycemia. However, in type 2 diabetes mellitus, the kidney lesions are strongly intertwined with changes dependent on the frequent pre-existence and concordance of obesity, dyslipidemia, and hypertension, as well as those generated by aging. Since the long evolution over the years of type 2 diabetes mellitus and natural aging both contribute to kidney injury, it is difficult to discern which of the mechanisms associated with each case is predominantly responsible for the development of histopathological changes, as well as how much of each clinical manifestation corresponds to diabetes or other mechanisms of kidney injury. Regardless of what has been previously said, CKD is a major complication of diabetes mellitus, and its clinical manifestations and possibilities of progression are as varied as the mechanisms that cause it.

CKD is defined as the persistence of urinary protein loss or GFR below 60 ml/min/1.73 m^2 for 3 months or more.

Albuminuria has been considered the distinguishing feature of diabetic nephropathy and, in general, a predecessor of the drop of GFR [12]. That is why it has had a central role in both early detection and proper management of CKD in diabetic patients [13]. However, increasing evidence suggests that the decrease in GFR can occur in the absence of albuminuria [14], especially in type 2 diabetes mellitus [15–20], which does not allow the influence that other factors may have in these cases of persistent hyperglycemia to be accurately established. That is why albuminuria and reduction of GFR should be considered as complementary manifestations of nephropathy. Both alterations may, or may not, overlap during kidney damage in diabetes mellitus [21].

8.2 Relevant epidemiological information and forms of presentation

The preference is to refer to the prevalence of CKD in diabetic patients as opposed to "diabetic nephropathy," given the uncertainty over which of the renal changes found in these patients are effectively due to diabetes mellitus, as has been previously stated. We believe that this unavoidable diagnostic difficulty constitutes a first limitation when defining the prevalence of kidney disease in this setting.

Another important limitation is the lack of well-designed studies where the prevalence of both proteinuric and non-proteinuric CKD associated with diabetes mellitus is systematically evaluated in properly selected populations. A final limitation – but no less important – is that not all prevalence studies are performed by assessing the protein or albumin loss with the same methodology and cut-off values, nor by evaluating kidney function with the same indicators, including different standardized creatinine (or other metabolites) measurements methods, as well as various formulas for GFR estimations. Consequently, prevalence may considerably differ as a result of this methodological heterogeneity. These difficulties are exacerbated in elderly diabetic populations since other factors impact on the above measurement values, such as lower plasma creatinine levels due to decreased muscle mass.

With these limitations in mind, studies show that the prevalence of CKD in diabetic patients varies between 37% and 40% when it is associated with the presence of proteinuria and/or with a drop in GFR <60 ml/min/1.73 m^2. Similar prevalence has been found in diabetic primary care patients [22–25] (Figure 8.1).

The prevalence of CKD in diabetic patients is about 2.5 times higher than among non-diabetic subjects of the same age. Studies that evaluate the prevalence of CKD associated with diabetes mellitus show that in

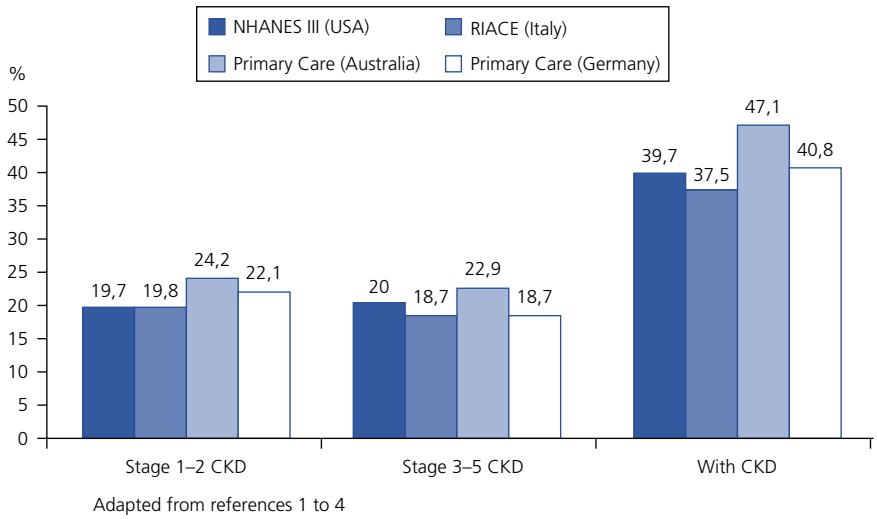

Figure 8.1 Reported prevalence of CKD in adult diabetic patients. Adapted from [1–4].

recent years, while in type 1 diabetes mellitus it has appeared to decrease, in type 2 diabetes mellitus it is not so clear that the same thing is happening. While proteinuric nephropathy decreases, non-proteinuric nephropathy seems to increase. This is particularly evident in CKD associated with the elderly [26, 27].

As for urinary protein loss, which is an earlier clinical manifestation of diabetic CKD, prevalence and clinical evolution seem to have changed in recent years. For decades urinary protein loss was a distinctive component of diabetic nephropathy in most clinical presentations. In the last few years, and as a result of various factors which are not yet entirely clear, loss of kidney function has become more frequent in diabetics, with no concomitant existence of significant urinary protein loss. Figure 8.1 shows that half of patients with CKD have a GFR < 60 ml/min/1.73 m^2; but a significant percentage of them show normal albuminuria levels. The Renal Insufficiency And Cardiovascular Events (RIACE) study showed that 29.6% of diabetic patients presented CKD, stage 3 to 5, and less than half had albuminuria (macroalbuminuria 12.8% and microalbuminuria 30.8%). Among the patients with low GFR, 43.2% had neither albuminuria nor diabetic retinopathy [28]. These results are also reflected in other studies, such as the primary care study performed in Germany [24] where 46% of the patients had GFR < 60 ml/min/1.73 m^2 without albuminuria. Other studies report similar data [29–31], reaffirming the fact that the loss of kidney function – without albuminuria as a component of CKD for diabetic patients – has a frequency similar to that of proteinuric renal disease.

The most relevant potential explanations for the above changes in clinical behavior are:

- the massive use of renin-angiotensin-aldosterone system (RAAS) blocking drugs known to be anti-proteinuric beyond their antihypertensive effect [26, 27, 32, 33]
- the improvement in glycemic and lipidemic control, and better management of arterial hypertension [25].

In this regard, an adequate glycemic control is important in reducing microvascular damage, but has a more limited influence over the loss of kidney function where there are other relevant factors involved, such as age, metabolic disorders, and high BP, which contribute to the development of glomerular and tubulointerstitial sclerosis.

This hypothesis is supported by the fact that the prevalence of proteinuric CKD associated with diabetes mellitus is much more prevalent in patients under 55 year of age, whereas in elderly patients there is a predominance of non-proteinuric nephropathy [25].

In other words, in older people, the non-proteinuric form of diabetes mellitus-associated CKD prevails, allowing for particular characteristics in terms of both

the potential and also rate of disease progression, prognosis and treatment strategy, choice of drugs, and therapeutic targets. In addition, special consideration should be paid to the increased risk of side effects and scant evidence relative to the benefits with intensified treatments [34].

It is important here to point out the weakness of the definition of old age based solely on a chronological scale. At the same age, it is not the same to be a healthy, active elderly diabetic, and to be a person who depends on help for daily activities, with physical or cognitive impairment and fragility due to poor health.

8.3 Pathophysiological mechanisms involved in diabetic kidney disease

The structural lesions produced in the kidney by diabetes mellitus are varied and complex, especially in type 2 diabetes mellitus, where the heterogeneity of the damage is vast [35–37] (Table 8.1). Table 8.1 shows a way of grouping the mechanisms involved, keeping in mind that there are strong interactions among them, and that their relative relevance often differs from patient to patient. The glomerular alterations, particularly those of the filtration barrier, have been well studied, becoming the paradigm of the DKD. There is discrepancy among different authors as to which of the three components of the filtration barrier would be most affected, thus the endothelium of glomerular capillaries, the mesangial matrix, and epithelial cells or podocytes have disputed their supremacy.

Injuries may also appear in other kidney structures, such as the tubulointerstitium and kidney vessels, which may also be severely damaged. However, nowadays it is frequent to find tubulointerstitial lesion without the classic glomerular injury and albuminuria [37]. It is very important to consider renal diabetic patients' lesions as a whole and as a result of multiple interacting molecular mechanisms [38].

Many modifiable factors influence the development and progression of diabetic renal damage. The most studied are hyperglycemia, hypertension, obesity, sedentary lifestyle, and smoking. There are also other factors over which we have no influence, such as genetic load and age.

Table 8.1 Pathophysiological mechanisms implicated in diabetic nephropathy.

Metabolic changes	**Hemodynamic modification**
Hyperglycemia	High blood pressure
Oxidative stress and glycation	Hyperfiltration
Phospholipids alterations and hyperuricemia	Glomerular hypertension
General factors and habits	Ischemic and hypoxic injury
Hereditary factors	**Hormonal activities**
Low physical activity/obesity	RAAS activities
Smoking	Vitamin D deficiency
Inflammation	Catecholamines
Aging	Endothelins

RAAS, renin–angiotensin–aldosterone system.

8.4 Metabolic alterations, particularly hyperglycemia

Control of carbohydrate metabolism alterations primarily helps to avoid, delay and minimize the appearance of renal lesions and complications in diabetic patients [39]. However, since the strict control of plasma glucose is difficult to achieve, cell dysfunction and metabolic changes appear, which in turn trigger several cell signaling pathways, promoting renal tissue and organ injury. The consequent oxidative stress (OS) and inflammatory process, favor the development of diabetic nephropathy [40–42]. The release of inflammatory cytokines may in turn stimulate cellular mechanisms that exacerbate OS, constituting a vicious cycle of injury.

The hyperglycemic environment along with the participation of humoral, hormonal, and cellular factors contribute to generate a substantial increase in the production of reactive oxygen species (ROS), particularly of superoxide anion and peroxynitrite, which can consume the antioxidant defenses.

8.4.1 Increase of polyol and hexamine contents

Due to hyperglycemia, tissue polyol increases more than 10 times [43]. The production of sorbitol is associated with a significant drop in antioxidant defenses,

especially of reduced glutathione. Elevated hexosamine levels generate metabolic changes by modifying the composition of certain proteins, and by activating some transcription factors and increasing the expression of plasminogen activator inhibitor type 1 (PAI-1) and transforming growth factor β1 (TGF-β1), all of which promote inflammatory process and fibrotic tissue changes [44, 45].

8.4.2 Activation of protein kinase C

A chronic activation of protein kinase C (PKC) occurs during the diabetic process. PKC belongs to an enzyme family that modulates the activity of other proteins. The increased PKC activation is associated with higher vascular permeability, extracellular matrix synthesis, cellular growth and apoptosis, angiogenesis, leukocyte adhesion, and modulation of cytokines [46].

8.4.3 Increase in advanced glycation end products

A chronic hyperglycemic state leads to an increase in the level of these metabolites, which interfere with cell function and stimulate the production of TGF-β1, one of the main factors responsible for glomerular sclerosis and tubulointerstitial damage [47]. In addition, advanced glycation end products (AGEs) stimulate ROS production [48].

8.4.4 Increase in oxidative stress

The changes listed above lead to severe OS [49, 50]. Abundant evidence obtained in animals [41, 51, 52] and diabetic individuals [53, 54] shows that renal ROS generation outweighs the capacity of the antioxidant defenses, leading to extensive oxidation of lipids, carbohydrates, proteins, and nucleic acids. Hyperglycemia also favors the generation of fatty acids, which further stimulate OS [55]. Consequently, many factors and pathways are affected:

a) increase in glucose transporter type 1 contents (GLUT 1) and TGF-β1 production in mesangial cells, which facilitate glucose entry, collagen deposition, cell apoptosis, and tissue fibrosis [56]

b) increase in platelet-derived growth factor (PDGF) production, which by interacting with TGF-β1 modulates mesangial growth and stimulates the interstitial matrix [57]

c) increase in connective tissue growth factor (CTGF), which plays a key role in kidney remodeling by increasing the production of fibronectin, collagen type I and IV, and mesangial cell hypertrophy [58, 59]

d) production of angiotensin II (Ang II), which – as we shall see further on – is a growth factor that plays a very active role in both hemodynamic and non-hemodynamic mechanisms. Ang II is a potent proinflammatory and profibrotic agent, mainly by stimulating ROS generation, particularly of mitochondrial origin, as well as the activity of nuclear transcription factor such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and the expression of TGF-β1 and other proinflammatory cytokines and chemokines [60, 61].

In the kidney, endothelial cells [62], the mesangium [63], and podocytes [64, 65] are all particularly affected. Other tissues are also affected, such as retinal cells, Schwann cells, and peripheral nerve neurons.

Endothelial cells do not require insulin for glucose uptake, therefore as a result of increased intracellular glucose and ROS levels the pro-apoptotic cascade increases through the translocation of bcl-2-like protein 4 (Bax) and down-regulation of anti-apoptotic B-cell lymphoma 2 (Bcl-2), which favors endothelial cell apoptosis by stimulating caspase-3 [66, 67]. Ang II contributes to this apoptotic mechanism [68].

Deficiencies in podocyte number and functionality are recognized as determinants in the progression of DKD [69]. Several of these alterations in the cellular functions are toxic to the podocyte and the main mechanism involved depends on the accumulation of ROS that favor detachment and apoptosis of these cells.

Injury to the tubulointerstitium involves infiltration with fibroblast and the associated inflammatory process, as well as the trans differentiation of epithelial cells into myofibroblast. In addition, the tubulointertitium is infiltrated with circulating mononuclear and polymorphnuclear leukocytes, which are attracted by stimuli of the diabetic environment and the OS generated. There is also rarefaction and loss of peritubular capillaries, which intimately correlates with the loss of function [70] and progression of kidney disease [71].

While the structure of the mesangium grows and expands, there is a simultaneous reduction in the glomerular capillary network that is the basis of the "chronic hypoxia theory" raised by Fine *et al.* [71], where the loss of glomerular capillaries by the primary injury reduces the flow in the postglomerular capillaries, generating hypoxia in the tubulointerstitium and

OS with apoptosis in epithelial cells, together with infiltration of inflammatory cells and fibrogenic response. This exacerbates capillary loss and the vicious circle that favors the progression of structural and functional lesions of the disease.

8.4.5 Other metabolic alterations

There are other metabolic alterations that are interrelated with derangements in carbohydrate metabolism such as dyslipoproteinemia and hyperuricemia, which have an important role in both oxidative changes and the generation of renal lesions.

8.4.5.1 Dyslipoproteinemia

Patients with diabetes mellitus show altered lipids and lipoproteins contents. They predominantly present hypertriglyceridemia, lower high-density lipoproteins, and increased very low-density lipoproteins (VLDL). They also present increased small and dense lipoprotein particles, with low apolipoprotein A-1 (apo A1) levels [72]. Several studies have found an association between kidney damage and decline in renal function [73, 74]. The concept of glomerular atherosclerosis, which in diabetes is accompanied by tubulointerstitial injury in association with lipid alterations, contributes to phenotypic diversity, in particular in patients with type 2 diabetes where non-proteinuria presentations are predominant [75, 76]. Some studies show a connection between hyperlipoproteinemia, OS, inflammatory cells, and mesangial injury, where the RAAS plays a dominant role as an enhancer of the process.

8.4.5.2 Alterations of uric acid

High uric acid plasma levels are known to be related to insulin resistance [77] as well as to other metabolic syndrome components, particularly lipid alterations [78]. Elevated uric acid levels, even if they are borderline, influence the development [79] and progression [80, 81] of CKD among diabetic patients. An increase in the activity of xanthine oxidase (the enzyme that transforms hypoxanthine-xanthine to uric acid) has been proposed as a potential mechanism responsible for the process. At the same time, this xanthine oxidase produces ROS (being one of the main sources), which can promote inflammatory responses in various tissues, including the kidney [82]. From the early stage of the disease elevated levels of uric acid have been consistently associated with the mechanisms of injury and progression of DKD.

Apart from the alterations in the kidney, DKD is associated with alteration in other systems, particularly the cardiovascular system, but we will not go into details of this in this chapter.

8.4.6 Changes in renal hemodynamics, inflammation, and hormonal influences

Important derangements in systemic, intrarenal and intraglomerular hemodynamics occur in DKD. The major components are: increased BP and vascular stiffness, increased pulsatility and intraglomerular pressure, hyperfiltration, and ischemic changes, in both glomerular and interstitial structures.

8.4.6.1 Increased shear stress in the glomerular structure

This is the result of a series of modifications, the most studied of which are (1) an increase in the transmission of the systemic pressure to the glomerular structure as a result of dilation of the afferent arteriole leading to (2) an increase in the intraglomerular pressure due to higher blood flow in the remaining glomeruli and the predominance of a vasoconstrictor tone in the efferent arterioles over the afferent arterioles, and (3) greater pulsatility index of the capillaries, due to dilation of the afferent arteriole accompanied by changes in the structure of medium and large arteries (vascular stiffness) and increased systolic BP. The elevation of shear stress generates an increase in the production of growth factors – including TGF-β1 – collagen and fibronectin, which promote the growth of the glomerular extracellular matrix [83, 84] and increased permeability of glomerular barrier to proteins [85].

8.4.6.2 Chronic inflammation

In spite of the fact that type 2 diabetes mellitus is considered a non-immune disease, there is growing evidence of the involvement of immune inflammatory processes and its micro- and macrovascular complications, including nephropathy [86, 87]. Tumor necrosis factor alpha (TNF-α) is cytotoxic to kidney cells and contributes to the alterations observed from the early stages of diabetic kidney injury [88]. Monocyte chaemoattractant protein-1 (MCP-1) and intercellular adhesion molecule-1 (ICAM-1) also contribute to kidney damage through inflammatory cell recruitment [89, 90]. Lymphocytes, monocytes, and macrophages are involved in diabetic kidney injury [91, 92] and

inflammatory markers such as IL-1 and lL-6 contribute to renal tissue damage [93].

Inflammation has acquired such relevance in the diabetic-related nephropathy that it is considered the main responsible factor for renal injury and the progression of kidney disease. Consequently, inflammation is one of the topics with the most abundant research and number of publications [94–97] where great therapeutic expectations have been made, despite the current lack of conclusive results.

8.4.6.3 Renin-angiotensin aldosterone system

Nowadays, the central role the RAAS has in kidney disease and particularly in DKD is well recognized. It is the most investigated medical subject and also the one with greatest development in the last century in terms of intervention strategies. The importance of this point is such that blocking the RAAS is the preventive pharmacological strategy universally used in these patients [98], with more than 20 years of massive use. Ang II is the most studied molecule of this hormonal cascade. It is in high concentration and activity in the renal parenchyma during DKD, being mainly responsible for the hemodynamic changes referred to previously. In particular, it increases the tone of the efferent arteriole, fostering increased intraglomerular pressure and leading to mesangial and tubular epithelial cell hypertrophy [99]. In addition, it has a systemic pressor effect by acting on the vascular smooth muscle, and has proinflammatory properties. Ang II favors apoptosis and promotes the production of TGF-β and MCP-1, two pro fibrotic cytokines involved in the process of glomerular and tubulointerstitial sclerosis [40, 100].

Another important member of this hormonal cascade is aldosterone, which plays an important role in the development of insulin resistance and tissue alterations in diabetes. Its relationship with vascular diabetic alterations has been widely studied, being co-responsible for the generation of OS and inflammatory processes. It is well known that blockade of mineralocorticoid receptors, upon which the aldosterone acts, has a powerful antifibrotic tissue effect, which includes the renal parenchyma [101].

Other hormonal systems interacting with the RAAS also influence the initiation and progression of kidney disease. The most studied of these are described below.

8.4.6.4 Vitamin D deficiency

There is growing evidence in animal and human studies that vitamin D deficiency is a risk factor for the development of type 2 diabetes mellitus. Vitamin D seems to be involved in β cell dysfunction and insulin resistance, especially that associated with obesity and the activation of the inflammatory cascade and the progression of kidney disease [102]. There are also a number of studies that show a close interrelationship between vitamin D deficiency and the RAAS hyperactivity [103]. The hypothesis is that both manifestations may represent two sides of the same coin. Both Ang II and vitamin D share phylogenetic evolution and ubiquity in multiple cells with co-localization of receptors in the cellular structures. Vitamin D deficit, in conjunction with Ang II, favors renal structure injury (by oxidative stress, inflammation, and fibrosis) and complications in type 2 diabetes mellitus [104].

8.4.6.5 The autonomic nervous system (sympathetic and parasympathetic) imbalance

The importance of alterations in the structure and function of the nervous system is well known, resulting in diabetic neuropathy [105, 106], but little is known about how an inadequate sympathetic/parasympathetic balance influences kidney disease. Down-regulation of the parasympathetic branch is the first change shown by the autonomic nervous system that leads to the preeminence of the sympathetic branch; in addition, the latter is hyperactivated in response to changes in blood glucose levels. Sympathetic hyperactivity not only alters other metabolic parameters by interacting with regulatory hormones and other systems such as the RAAS, the endothelins (ETs), leptins, and OS, but also affects lifestyle habits, such as quantity and quality of sleep, the obstructive sleep apnea syndrome, and sodium intake among others [107, 108]. It is obvious that all this leads to changes in the structure and function of the kidney [109, 110].

8.4.6.6 The endothelins

Increased ET levels in the kidney, especially ET1, participate in DKD. By stimulating ET receptor A (ETA) ET1 increases the production of ROS and in turn the increase in OS generated by diabetes mellitus enhances ET production, which after binding ETA causes inflammation and glomerular lesion with albuminuria, independently from BP. ET1 dependent renal injury can also be produced through different pathways [111–113].

8.4.7 Main mechanisms that lead to renal lesions

We have left for last the discussion of the mechanisms that we consider of greatest impact in order to treat them as a whole: the genetic burden, lifestyle and diet, central obesity, hypertension, and aging. It is obvious that all these factors interact with one another and in some cases are part of the causal phenomena described previously.

8.4.7.1 The genetic load and fetal programming

These are a consequence of clinical situations and maternal habits [114, 115], both during pregnancy and the early childhood years [116], and together with the family history of the disease are decisive factors for the initiation and progression of CKD favoring the DKD [117, 118]. Inappropriate habits, especially when there is an unfavorable genetic load, deserve special attention from the first years of life.

8.4.7.2 Inadequate lifestyle and habits

Lifestyle and habits such as the lack of regular physical activity and an unhealthy diet (not only in terms of the content and type of carbohydrates ingested but also in terms of low intake of fiber, fruits, and vegetables, and excessive intake of saturated fats, alcohol, and salt) along with smoking are determinants for nephropathy. Improvement in this inappropriate lifestyle and habits, as we shall emphasize later on, exceeds any other possible strategy in terms of avoiding the appearance of metabolic derangements, and the initiation and progression of kidney disease and its complications. These factors also reduce natural defenses (antioxidant defenses, sirtuines), along with functional reserves and tissue/organ elasticity [119].

8.4.7.3 Obesity

Central obesity and hypertension in the context of the development of type 2 diabetes mellitus are generally simultaneous events that are often present several years before the onset of the disease. In the vast majority of type 2 diabetes mellitus patients who develop nephropathy both manifestations were already present [120].

From the early stages of the disease, obesity generates hyperfiltration, enlargement of the glomerular mesangium with expansion and thickening of the basement membrane, and some degree of glomerular sclerosis. Alterations in the albumin/creatinine ratio are much more frequent in obese patients than in the slim population [121, 122]. Obesity is associated with higher production of cytokines, adipokines, proinflammatory mediators (TNF-α, IL-6, MCP-1), and fibrotic mediators (TGF-β), as well as increases in leptin levels and vasoactive substances in an oxidative environment together with low levels of adiponectin [123]. It is evident that these changes do not differ significantly from those described in the early stages of diabetes mellitus, to such an extent that it is often difficult to distinguish between the histological alterations present in obesity and diabetes mellitus, nor are there significant differences in the pathways involved [124].

8.4.7.4 High blood pressure

High blood pressure is present in more than 90% of type 2 diabetes mellitus patients that present nephropathy [125]. Hypertension is considered the main factor responsible for the emergence of nephropathy in diabetic patients. The absence of both persistent hypertension and retinopathy in type 2 diabetes mellitus patients with renal disease points to other underlying causes for the nephropathy that need to be uncovered [126].

Arterial hypertension is one of the recognized mechanisms underlying chronic renal damage in a hyperglycemic environment. The hemodynamic changes produced generate or amplify a hyperfiltration state accompanied by increases in shear stress and glomerular pulsatility, favoring protein loss and the inflammatory and fibrotic mechanisms already described [83, 84]. These changes, in conjunction with hormonal changes such as high Ang II and endothelin activity, and changes in the sympathetic system already referred to, are partners in the glomerular changes, glomerular collapse, or consolidation of the glomerulus and focal segmental glomerulosclerosis [127, 128].

The precise origin of kidney lesions is difficult to define since it should be kept in mind that high BP alone can produce similar changes, characterized by predominance of glomerular obsolescence, and recognized by glomerular collapse and intracapsular fibrosis, as well as by ischemia, which is favored by atherosclerosis of preglomerular vessels [129, 130]. The concomitant process of post-glomerular ischemia and tubulointerstitial inflammation generates the slow deterioration of renal structure and function known as nephroangiosclerosis. Although glomerular consolidation changes have been described in hypertensive nephropathy, they are much less frequent than in diabetes mellitus. Clinically,

hypertensive kidney lesions tend to be less proteinuric. Nephroangiosclerosis, as proposed by Kincaid-Smith's hypothesis, cannot be attributed only to hypertension but to the conjunction with many associated factors [131], such as race, gender, genetic load, low birth weight, postnatal obesity, and metabolic changes.

8.4.7.5 Aging

Finally, we must consider those kidney lesions that are a consequence of the aging process, which as we have mentioned are very similar and overlap with conditions described previously. According to the medical literature, age is one of the most influential factors in the occurrence of renal injury and loss of kidney function. Thus CKD is far more prevalent among the elderly. The fibrotic lesions that replace normal kidney tissue are common in people over 65 and progress with age [132, 133]. Glomerulosclerosis, tubular atrophy, interstitial fibrosis, and atherosclerosis occur together as part of a common process that accompanies kidney aging. This occurs in both healthy animals [7, 8, 134] and human beings in apparent good health [135, 136]. When other factors are added to natural aging, such as the presence of diabetes mellitus, hypertension, obesity, and other metabolic alterations, there is an acceleration of the natural kidney aging process, usually involving the appearance of few specific lesions. This is due to the fact that most of the above pathologies involve the same pathway of injury and intracellular mechanisms as aging and they increase the speed at which the aging changes occur, at the same time as the body's defense mechanisms are overwhelmed and consumed. The age-related decline of the body's defenses exacerbates that generated by diabetes mellitus, kidney disease, and the other components of the illness.

Figure 8.2 summarizes the concepts presented in this text, showing the complexity of the multiple mechanisms involved which interact with variable predominance according to the condition being considered. We have tried to reproduce a real case scenario for patients with type 2 diabetes mellitus who have kidney disease associated with several other factors, thus determining the different clinical presentations.

8.4.8 Screening and diagnosis of DKD

The search for chronic kidney injury in diabetic patients should be performed systematically and in a simple, effective, and inexpensive way. It is important to assess urinary protein loss, especially albumin as a marker of renal injury, and kidney function through GFR estimation.

8.4.8.1 Albuminuria

Loss of urinary albumin must be investigated annually once type 2 diabetes mellitus has been diagnosed and after 5 years of diagnosis of type 1 diabetes mellitus.

In the search for kidney damage, 24-h urine samples can be used. However, a single sample of the first morning urine (to avoid postural albuminuria) is recommended since it is simply collected and has an excellent correlation with 24-h data. With this sample study, the relation between urinary albumina and creatinine is estimated (albuminuria/creatinuria ratio expressed in mg/g or µg/mg). The most frequent causes of abnormal results not related to diabetic kidney disturbance should be excluded, including intense physical activity on the previous day, fever, hematuria or coincidence with menstrual bleeding, severe high BP, genital or urinary tract infection, congestive heart failure or acute intercurrent disease. The persistence of urinary protein loss or decreased kidney function for at least 3 months is necessary to confirm the existence of CKD.

Categories of albuminuria levels

Normal: urinary albumin/creatinine ratio < 30 mg/g

Albuminuria (previously microalbuminuria): urinary albumin/creatinine ratio 30–300 mg/g

Proteinuria (previously macroalbuminuria: urinary albumin/creatinine ratio > 300 mg/g [137]

A confirmed result above normal albuminuria levels in a diabetes mellitus patient does not necessarily indicate that this value is an expression of the presence of diabetic nephropathy. In fact, the concomitance of hypertension, frequent in diabetes mellitus, can be a cause of elevated values of proteinuria. Abnormal, but not very high, levels of the albumin-creatinine ratio are frequent in both high BP and elderly type 2 diabetes mellitus patients. However, in type 1 diabetes mellitus patients with 5 or more years of diagnosis, absence of comorbidities, and in presence of reduced GFR or diabetic retinopathy, it is reasonable to etiologically associate proteinuria with the coexistence of diabetic nephropathy [138, 139].

The use of test strips to establish proteinuria is a possible screening method in the absence of a conventional laboratory, especially in the field of primary health care.

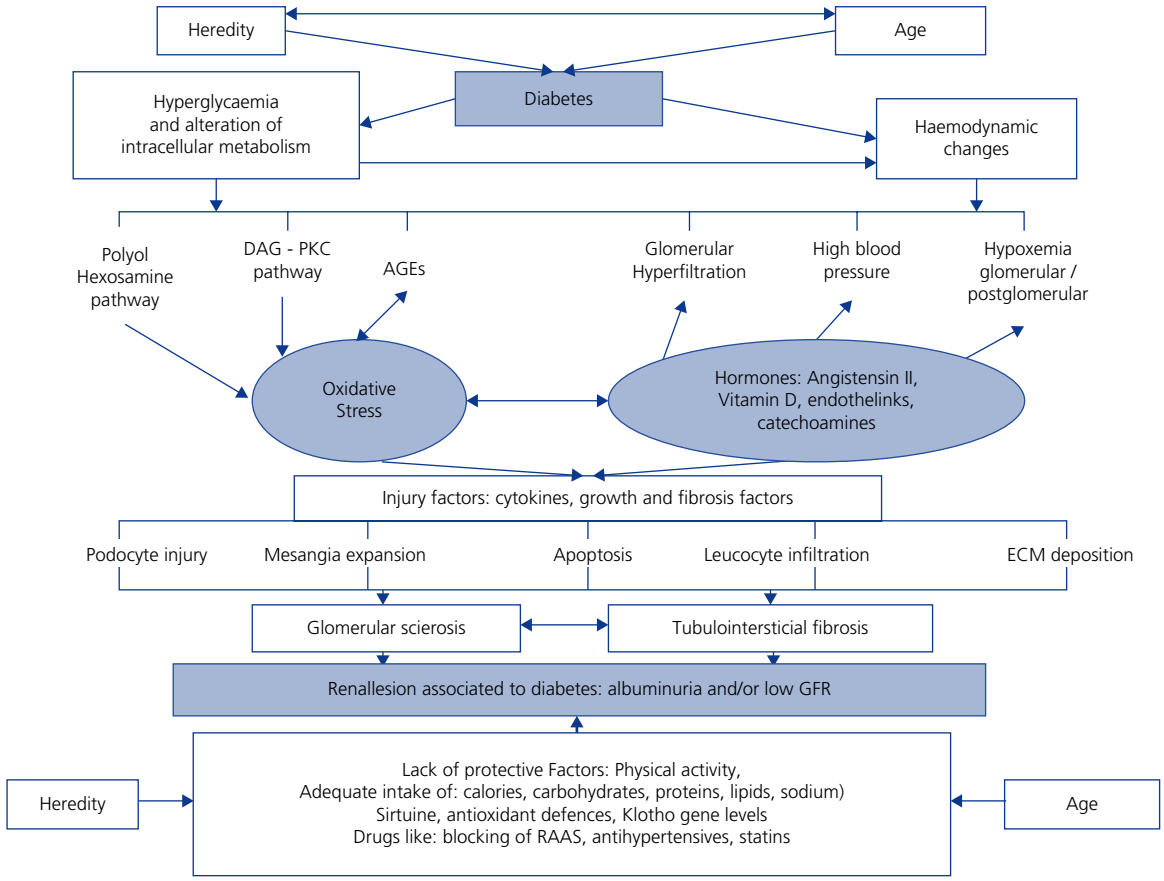

Figure 8.2 Pathophysiological mechanisms in diabetic kidney disease.

The sensitivity of this method allows trace protein levels to be detected when values are between 150 and 500 mg/g urinary protein/creatinine ratio and the results are reported as positive when >500 mg/g. Test strips do not detect moderate losses of albumin and the lack of specificity does not discriminate between albuminuria and proteinuria [137]. Test strips with better accuracy are also available and they are useful as they could complement the previously mentioned screening strips in detecting lower levels of albumin, up to 30 mg/g creatinine. However, we must remember that the diagnostic confirmation of positive albuminuria must be made using a quantitative measurement method.

8.4.8.2 Glomerular filtration rate

Screening for DKD includes the annual determination of plasma creatinine level, a frequency that can be increased in some clinical situations. Plasma creatinine is used to assess kidney function, but it should be taken into account that gender, race, age and muscle mass introduce variability to these parameters.

Various guidelines advise the estimation of GFR based on serum creatinine level to be performed by using the formula proposed by the Modification of Diet in Renal Disease Study Group (MDR-4) [140] or the Cockroft–Gault equation [141].

These formulas have some weaknesses since they lose sensitivity when evaluating normal kidney function and in stage 2 of GFR. In these cases it is recommended that results are reported as >60 ml/min/1.74 m^2. This is particularly important in patients over 70 years of age or with reduced muscle mass, a particularly frequent finding in type 2 diabetic patients. A new formula has been proposed in order to improve this situation: The Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) equation. Although it is more accurate and has been

Table 8.2 Chronic kidney disease stages based on eGFR measurements (adapted from [145]).

	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5
Functional situation	Normal or hyperfiltration	Mild reduction	Moderate reduction	Marked reduction	Severe reduction	Kidney failure
eGFR (ml/min)	130–90	89–60	59–45	44–30	29–15	14–0

eGFR, estimated glomerular filtration rate.

validated in some populations, it has not yet been universally adopted [142, 143].

The evaluation of kidney function by other means not involving creatinine, especially in diabetes mellitus patients, has acquired special importance. Thus, GFR can be estimated (eGFR) based on the measurement of cystatin C administered exogenously. The drawback of this method is its lack of availability and high cost, which make it inaccessible for widespread use at this time [144].

With the information obtained from the eGFR we can define CKD stages according to Table 8.2.

Although the definition of the stages of kidney function provides very useful information in itself, it furnishes little information about the risk of progression of CKD in patients with diabetes mellitus. For that reason the best way to estimate risk progression is by using both GFR and albuminuria. The Kidney Disease/Improving Global Outcomes guideline (KDIGO) combines eGFR and albuminuria, and defines the risk of progression, as shown in Table 8.3.

Table 8.3 The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline (adapted from [146]).

Risk	Albuminuria	Filtration
Mild	Normality (<30 mg/g Cr) Albuminuria (30–300 mg/g Cr)	Stage 3a Stages 1 and 2
Moderate	Normality(<30 mg/g Cr) Albuminuria (30–300 mg/g Cr) Proteinuria (>300 mg/g Cr)	Stage 3b Stage 3a Stages 1 and 2
High	Normality(<30 mg/g Cr) Albuminuria (30–300 mg/g Cr) Proteinuria (>300 mg/g Cr)	Stage 4 Stages 3b and 4 Stages 3a and 3b
Very high	Normality(<30 mg/g Cr) Albuminuria (30–300 mg/g Cr) Proteinuria (>300 mg/g Cr)	Stage 5 Stage 5 Stages 4 and 5

8.4.9 Diabetes and nephropathy: macro- and microvasculopathic impact

8.4.9.1 Macrovasculopathy, diabetes, and kidney disease

In the general population the presence of a reduction in GFR has a clear impact on mortality for all causes and in particular on cardiovascular mortality. Thus, a follow-up study of outpatients in the USA found that the rate of cardiovascular mortality adjusted by age rose from 2.11/100 patients per year for those with GFR ≥ 60 ml/min to 3.65, 11.29, 21.87, and 36.60/100 patients per year in filtration reduction stages 3a, 3b, 4, and 5, respectively. In the same study, the hazard ration (HR) (95% CI) for death from all causes adjusted for multiple variables vs GFR ≥ 60 ml/min was 1.20 (1.10–1.20), 1.80 (1.70–1.90), 3.20 (3.10–3.40), and 5.90 (5.4–6.5) in filtration reduction stages 3a, 3b, 4, and 5, respectively [147].

According to data obtained from the National Health and Nutrition Examination Survey (NHANES III), in the diabetic population the coexistence of albuminuria with a reduction in GFR increased the cumulative incidence adjusted for age, sex, race, smoking, BP, and cholesterol (95% CI) to 23.4% (17.2–19.6) for total mortality and to 16.2% (11.120.9) for cardiovascular mortality vs the non-diabetic population without nephropathy. When analyzing this data for the presence of albuminuria alone, the increase in death for all causes was somewhat lower (17.8%), but when both components of CKD coexisted, the increase in death relative to diabetic patients without nephropathy amounted to 47% [148].

Analyzing the macrovascular events separately [149], the incidence rates (100 patients/year) in the diabetic population without CKD vs the diabetic population with CKD were 3.2 and 6.9 for myocardial infarction, 13.1 and 22.0 for stroke/TIA, and 18.8 and 26.6 for peripheral vascular disease (PVD) respectively. When compounding the occurrence of myocardial infarction,

Table 8.4 Data from three key studies in type 2 diabetes showing diverse interventions with different levels of urinary protein loss.

Study	Age (years)	Duration of diabetes (years)	HbA1c (%)	SAP (mmHg)	DAP (mmHg)	Albuminuria (mg/g)	Retinopathy (%)
[150]	57.3–59.4	NA	7.1–7.3	153	90	53.4–58.3	35.8–45.0
[151]	58.3–59.1	NA	8.1–8.2	159	87	1000.0–3800.0	64.0–69.0
[152]	60.7	NA	8.5–8.9	152–153	82	1237.0–1261.0	61.7–65.8
[153]	26.7–27.9	5.5–5.8	9.1	114.5–114.6	72.9–73.1	10.0–11.7	48.2–51.0

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; NA, not available.

stroke or PVD in diabetes mellitus patients, the incidence of composed cardiovascular events was doubled in the presence of CKD (25.3 vs 49.1).

8.4.9.2 Microvasculopathy, diabetes, and kidney disease

In order to obtain information on this less explored topic, we reviewed information from randomized, controlled studies for kidney disease data and its association with the most identifiable of the microvascular diseases: diabetic retinopathy (DR) in both type 2 and type 1 diabetes mellitus.

Table 8.4 shows the result of three studies published in the same year that were conducted on type 2 diabetes mellitus patients of similar ages but receiving diverse intervention and with different levels of urinary protein loss (without data on duration of diabetes). Patients with albuminuria had a 40% lower prevalence of DR than those with proteinuria, but a limitation to this observation is that the degree of diabetic control in the group with albuminuria was better than in the others [150–152]. Table 8.4 also shows that young type 1 diabetes mellitus patients with normal levels of albuminuria, and glycemic control similar to that of type 2 diabetes mellitus proteinuric patients, present a similar incidence of DR. This indicates that microvasculopathy is associated with nephropathy in type 2 diabetes mellitus, whereas in type 1 diabetes mellitus this association is not necessarily present [153].

8.4.10 Treatment to be considered in older patients with diabetes with associated kidney disease

As the whole therapeutic area, both non-pharmacological and pharmacological, will be dealt with in other chapters of this book, we will only focus on the data that modulates interventions based on the coexistence of different degrees of CKD associated with diabetes in elderly patients.

8.4.10.1 Sedentary lifestyle and overweight

In regard to overweight, obesity, and central obesity it must be remembered that apart from the ample evidence pointing to the reduction of cardiovascular risk when weight is successfully controlled, obesity is associated with glomerulopathy.

8.4.10.2 Scheduled physical activity

While there is no evidence pointing to the association of physical exercise with a reduction in the progression of CKD, a program of aerobic activities, resistance, and elongation is required to attain the goal values for BP, lipids, HbA1c, and body weight, thus reducing cardiovascular risk and mortality.

8.4.10.3 Dietary plan

The dietary plan should take into account the frequent reduction of muscle mass in the older adult. In stages 1 and 2 of CKD there are no specific indications beyond those listed for type 2 diabetes mellitus, hypertension, dyslipidemia or elevated body weight patients. In stages 3 and 4 there should be a reduction in protein intake to between 1 and 1.2 g/kg body weight and in stage 3 prior to dialysis or transplantation to between 0.8 and 1 g/kg body weight. Protein intake is, in general, less restricted in the dialysis stage. Restrictions on foods rich in potassium (K) should be considered when the circulating levels are within the maximum values. It is important not to lose sight of the nutritional contribution of iron, folic acid, and vitamin B complex, which should be supplemented pharmacologically from stage 3. From stage

Table 8.5 Foods low in sodium, potassium and phosphorus.

Type of food	Examples
Cereals	Cooked rice, porridge, cooked soup, sweet potato, potato
Vegetables and fruits	Cucumber, asparagus, apple, pear, cherry, orange, tangerine, grapefruit, lemon
Legumes	Beans, chick peas, soybeans, lentils (up to twice a week)
Meats	Chicken breast, fish fillet boiled/roasted, beef entrails, cooked chicken
Dairy	Whole milk, soy milk, yogurt (maximum once or twice a week)
Oils and fats	Corn oil, soybean, canola, sunflower, mayonnaise, cream cheese, margarine, almonds, roasted peanuts, nuts, pistachio
Seasonings	Garlic and cinnamon powder, ginger, chamomile, mint, mustard, rosemary, basil, pepper, vinegar and vanilla
Liquids	Mineral water, tea without sugar, sugar free gelatin (consumption will depend on the patient's liquid retention)

4 dietary factors that may increase the circulating phosphorus must be checked. The use of non-calcium-containing phosphate binders is recommended.

A list of non-usually restricted foods in CKD [154] is given in Table 8.5.

8.4.11 Hyperglycemia in CKD in pre-diabetes

Taking into account the increase in mortality associated with impaired oral glucose tolerance [155] in CKD patients, it is convenient to take measures to limit the progression to diabetes while prioritizing non-pharmacological approaches in elderly patients [156, 157].

8.4.12 Hyperglycemia in CKD in diabetes

8.4.12.1 General considerations

According to the International Diabetes Federation for Older People Guidelines [158], glycemic goals should be individualized, considering if there is concomitance of co-morbidities (especially cardiovascular disease) and a history or risk of hypoglycemia, as well as the patient's functional status (functionally independent, for whom the HbA1c goal will be between 7.0 and 7.5%; functionally dependent, HbA1c between 7.0 and 8.0%; fragility or dementia coexist or if the patient is in the final stages of life, HbA1c up to 8.5%). It is critical to start pharmacological therapy by using low doses and to increase them with caution, discontinuing any ineffective medications or those of questionable usefulness. The main recommendation of the medication guide listed below is to prioritize the use of metformin, which is the drug of choice. Secondly, sulfonylureas (SUs) with low hypoglycemic risk or the dipeptidyl peptidase-4 (iDPP-4) inhibitors should be added. The third component (SUs or iDPP-4, whichever has not been used) is added when the goals have not been reached. An alternative to the third oral drug is the use of basal insulin (premix or NPH), maintaining metformin as oral therapy.

The different hypoglycemic drugs should only be used in patients with CKD when lifestyle changes do not result in the glycemic goals being reached [159]. It would be appropriate to review the medication considering the characteristics of the elderly patient.

8.4.12.2 Metformin

Metformin does not require adjustments in stages 1 and 2. In stage 3a, doses of 1500 mg/day or below are recommended. In Stage 3b dosage should be lowered by 50% for patients who were previously medicated, and metformin therapy is not to be started in those patients who have not previously taken it until that moment. Metformin must not be used in stages 4 and 5.

8.4.12.3 Sulfonylureas

Glibenclamide (glyburide) should not be administered due to its high percentage of active metabolites with renal excretion, which explains the high incidence of hypoglycemia occurring with this drug.

Glipizide may be used without adjustments until stage 3.

Gliclazide should be used in medium to low doses and must be avoided in stages 4 and 5.

Glimepiride should not be used in doses higher than 1 mg at any stage of CKD.

8.4.12.4 Meglitinides

Repaglinide does not require adjustments and *nateglinide* should not be used in stages 4 and 5 of CKD.

8.4.12.5 Inhibitors of the α-glucosidases

Acarbose is not to be used in stages 4 and 5 of CKD.

Thiazolidinediones

Pioglitazone may be used without any adjustments at any stage of CKD.

8.4.12.6 DPP-4 inhibitors

These may be used at any stage of CKD.

Linagliptin may be used with no adjustments.

Vildagliptin, *saxagliptin*, and *sitagliptin* doses should be reduced by half from stage 3.

Sitagliptin should be reduced to 25 mg in stages 4 and 5.

8.4.12.7 Glucagon-like-peptide-1 mimetics

Exenatide must be reduced to 5 mg/day in stages 2 and 3, and must be avoided in more advanced stages. Given that the experience with *liragutide* is limited in CKD, this compound should be avoided in this situation, and *lixisenatide* should be employed with caution from stage 2 onward. As weight loss is associated with the use of these drugs, elderly patients with reduced lean body mass should avoid them.

8.4.12.8 Sodium-glucose cotransporter 2 inhibitors

These inhibitors may be used in stages 1 and 2. They should not be used from stage 3 because they lose their effectiveness. Elderly patients with reduced lean body mass should avoid these inhibitors due to the weight loss associated with their use.

8.4.12.9 Insulin

Insulin must be titrated carefully due to increased risk of hypoglycemia from stage 4.

8.4.13 Hypertension in CKD and diabetes

8.4.13.1 General considerations

When addressing this issue we must keep in mind that both hyperglycemia and hypertension interact with each other, are enhanced by activation of the RAAS. This this activation, both systemic and intrarenal, facilitates the progression of albuminuria and the decline of the glomerular filtration [160, 161].

On the other hand, and as discussed at the beginning of this chapter, hyperfiltration, as an initial stage of nephropathy in diabetes, foretells further progression, both in type 1 and type 2 diabetes mellitus, to more advanced stages of the illness [162, 163]. Hyperfiltration improves when the intraglomerular pressure is reduced by pharmacological action on the RAAS.

Another fundamental point to be considered is that when BP is adequately controlled a noticeable benefit occurs regarding the emergence and/or speed of progression of kidney disease. In this context lowering BP is the main objective to fulfil and in most situations requires the use of two to four antihypertensive drugs. In recent years there have been controversies over which is the best target BP for diabetes mellitus patients, especially for type 2 diabetes mellitus patients over 65 years of age.

The experts who have been discussing this issue have not reached an agreement on this point, and their discrepancies are expressed in the different guides. It seems that in patients with diabetes and nephropathy, arterial pressure below 130 mmHg is not significantly beneficial, but apparently it increases the risk of events, including the progression of kidney disease. For the oldest diabetics under antihypertensive treatment, the benefits seem to decline once a systolic BP of 150 mmHg has been reached. Most of the recommendations suggest that the optimal value would be between 130 and 150 mmHg, always taking into account the patient's overall health, their degree of independence and the tendency to postural and postprandial hypotension, the latter of which is to be avoided because it greatly increases the risk of events. For the majority of patients this implies a target BP that lies around 140 mmHg. For more fragile patients with hypertension, a reasonable objective would be <150 mmHg without hypotension, and for younger patients without vascular damage and with clinically important proteinuria levels BP around 130 mmHg would be acceptable. The adequate diastolic pressure is suggested to be between 80 and 85 mmHg [164–170].

8.4.13.2 Action on the RAAS

Considering all the above, there is consensus that the drugs that act on the RAAS are of first choice or must be associated with other antihypertensive drugs in the treatment of hypertension associated with diabetic nephropathy, independently from their possible low dose use in patients with albuminuria and/or hyperfiltration with normotension to reduce the progression of kidney damage [169]. Ang II converting enzyme inhibitors (ACEI) or Ang II receptor blockers (ARBs) can be used, although a recent meta-analysis of controlled prospective studies in diabetic hypertensive populations suggests that ACEI could have better impact in terms of total mortality, cardiovascular disease and major events [171].

The combination of (ACEI) and ARBs, or the addition of a renin blocker, although more effective in terms of reduction of proteinuria, is not recommended for elderly type 2 diabetes mellitus patients due to the frequent existence of vascular damage, which could increase the risk of adverse events [172, 173].

8.4.13.3 Calcium-channel blockers, thiazide diuretics, and α-blockers

If the target BP is not reached with drugs that act on the RAAS, then any of these three drugs may be added. The third drug is used only if adequate doses of the second drug have not proven effective to achieve the target BP. In these patients, in whom it is very difficult to control high BP, aldosterone antagonists should be used with extreme caution due to the greater risk of hyperkalemia [174].

In hypertensive diabetes mellitus patients the association of calcium antagonists and RAAS blockers is frequently used when the target BP cannot be achieved. However, there are some discrepancies regarding the use of this drug combination when diabetes mellitus and hypertension are associated with CKD. The type of calcium-channel blocker to be used may be important given their different effects on intraglomerular pressure [175].

Frequently diabetes mellitus patients with CKD are resistant to antihypertensive treatment, that is, they do not achieve BP goals with the use of three antihypertensive drugs, one of which should be a diuretic. Evaluating and dealing with resistant hypertension is a complex area of management and is outside the scope of the current chapter [176].

8.4.13.4 Dyslipidemia in CKD and diabetes

We have already mentioned that in the general population there seems to be a progression of albuminuria and a reduction of GFR associated with dyslipoproteinemia [177]. Prospective studies suggest that as dyslipoproteinemia control criteria are ameliorated, the above association persists although somewhat reduced [178]. In addition, other evidence points to the association of kidney disturbances with high plasma cholesterol or low high-density lipoprotein (HDL), when they are accompanied with increased triglyceride levels [179, 180].

Although there are a number of observations in diabetic populations that indicate an association between dyslipoproteinemia and the progression of albuminuria and probably reduced GFR, data from the UK Prospective Diabetes Study (UKPDS) argues that dyslipoproteinemia is associated with increased albuminuria but not with GFR < 60 ml/min, nor with duplication of serum creatinine level [181].

Nonetheless it is obvious that intervention to correct dyslipidemia ensures a reduction in cardiovascular events that are much more prevalent in patients with CKD associated with diabetes.

8.4.13.5 Statins

Administration of atorvastatin in diabetic populations has been associated with discrete improvement in GFR that becomes more evident in those patients with elevated albuminuria [182].

8.4.13.6 Fibrates

According to a meta-analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Diabetes Atherosclerosis Intervention Study (DAIS) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study, which included 14,385 diabetic patients, fibrate administration significantly reduces the progression of albuminuria (RR 0.86) [183].

8.5 Conclusion

In older people, the association of kidney disease and diabetes is very frequent and the main cause is the damage inflicted on the kidney by metabolic alterations as well as by other associated factors such as aging, the concomitance of hypertension, persistent obesity for many years, other cellular metabolic alterations (hyperlipidemia, hyperuricemia, OS), and other influences that result from hormonal imbalance (RAAS, autonomic nervous system, leptin, hypoestrogenism, and hypoandrogenism).

The influence that lifestyle has on kidney damage must also be mentioned. When the treatment objective is reached, there is a modest reduction in the injury mechanisms, although in general there is still a very high residual risk. Perhaps the most important lesson we have learnt in the last few years is that in trying to reduce this residual risk by intensifying the pharmacological treatments (especially through access to the best possible glycemic control and reduction in BP),

we frequently expose patients to other risks that surpass the potential benefits and this issue is greater in older people. It is therefore essential to reduce the use of drugs of dubious effectiveness or need, as well as to identify the range of appropriate goals for each patient.

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CHAPTER 9

Visual loss in people with diabetes in old age

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KEY MESSAGES

- The World Health Organization states that 285 million people are estimated to be visually impaired worldwide and that 82% of these are over the age of 50.
- In the UK, the fastest growing age group is aged 85 and over and 1 in 3 people over the age of 85 in the UK are living with sight loss. In 2006 there was a concerning report about the increase in visual loss in the 65–74 years and 75–84 years age groups in the UK caused by diabetic retinopathy.
- In the developed world, the most common causes of visual loss in older people are refractive error, cataract, macular degeneration, diabetic maculopathy, and glaucoma.
- It is important that older people have access to appropriate optometry services for correction of refractive error and ophthalmology services for treatment as required for cataract, macular degeneration, diabetic maculopathy, and glaucoma.
- Smoking is a risk factor in many of these conditions and encouragement to give up smoking is an important public health message for eye health.

9.1 Introductions and background

There are different definitions of blindness and visual loss in different parts of the world. The definitions of blindness have often developed to assess whether an individual has sufficient vision to enable them to work.

Legal blindness (World Health Organization, WHO): Legal blindness is defined by the WHO as vision in the better eye of less than 20/400 or a visual field of less than 10 degrees in the better eye with best possible correction. The WHO defines "low vision" as visual acuity of less than 20/60 (6/18), but equal to or better than 20/200 (6/60), or visual field loss to less than 20 degrees in the better eye with best possible correction.

Legal blindness (USA): Legal blindness is defined in the USA as best corrected visual acuity in the better eye worse than or equal to 20/200 or a visual field extent of less than 20 degrees in diameter. Vision impairment is defined as having a best corrected visual acuity of 20/40 or worse vision in the better seeing eye.

Legal blindness UK: The definition of blindness and partial sight is defined in the UK as vision in the better eye of less than 3/60 or better than 3/60 but below 6/60 with a very restricted visual field. In 2005 the Certificate of Visual Impairment became the new form used in the UK (replacing the BD8) to register people as severely sight impaired (blind) or sight impaired (partially sighted). The definition of severely sight impaired (blind) applies to someone who while wearing glasses or contact lenses falls into any one of the following categories:

- visual acuity of less than 3/60 with a full visual field
- visual acuity between 3/60 and 6/60 with a severe reduction of field of vision, such as tunnel vision
- visual acuity of 6/60 or above but with a very reduced field of vision, especially if a lot of sight is missing in the lower part of the field.

In 2002, Foran reported from the Blue Mountain Eye Study that, of the 3654 older participants (>50 years) in the Blue Mountains Eye Study, after refractive

Diabetes in Old Age, Fourth Edition. Edited by Alan J. Sinclair, Trisha Dunning, Leocadio Rodríguez Mañas, and Medha Munshi.

correction, the proportion of incident bilateral impairment was steadily decreasing due to cataract because of successful treatment but was increasing due to age-related maculopathy. In 2003, Wang reported data from the Blue Mountain Eye Study in Australia that decreased vision may be a marker or contributing factor to subsequent nursing home placement in general older populations [1]. For each line of reduction in presenting visual acuity at baseline, there was a 7% increased risk of subsequent nursing home placement. However, this result was not substantiated in a UK study which concluded that the association between visual impairment and risk of nursing home admission was eliminated after controlling for a wide range of other confounding factors and co-morbidities [2].

9.2 Causes of visual impairment

In 2003 Congdon reported on the leading causes of visual impairment and blindness in the world and identified [3]:

1. refractive error
2. cataract
3. glaucoma
4. age-related macular degeneration (AMD)
5. infectious causes:
   - a. trachoma
   - b. river blindness (onchocerciasis)
   - c. cytomegalovirus in human immunodeficiency
6. vitamin A deficiency
7. diabetic retinopathy
8. trauma.

In 2006, Bunce reported on registration rates of blindness or partially-sighted in England and Wales during the year April 1999 to March 2000 [4]. The main cause of visual loss was ascertained where possible and compare to the last analysis conducted for 1990–1991 data. Of concern was a near doubling of the incidence of certifiable sight loss due to diabetic retinopathy in people over 65 years. The incidence recorded was an increase in the 65–74-year-old age group from 7.28 to 15.06 per 100,000 population and from 8.27 to 17.08 in the 75–84-year-old age group. One possible explanation given was that people with diabetes are living longer and this puts them at risk of developing the disabling consequences of the disease.

This increase was despite a report from the same group in 2014 that, for the first time in at least five decades, diabetic retinopathy/maculopathy was no longer the leading cause of certifiable blindness among working age adults in England and Wales, having been overtaken by inherited retinal disorders [5].

In August 2014 the WHO produced a factsheet on visual impairment (see Box 1) [6]. This stated that with an increasing elderly population in many countries, more people will be at risk of visual impairment due to chronic eye diseases and aging processes.

An excellent review of dementia and serious sight loss as undertaken by Professor Roy Jones and Dr Richard Trigg in 2007 supported by the Thomas Pocklington Trust [7]. The review concluded that it is possible to make a rough estimate that about 2.5% of people over the age of 75 in the UK are likely to have dementia and significant sight loss.

In 2008 Scanlon reported a prevalence of visual impairment (2.9%) and acuity blindness (0.45% UK or 0.7% WHO) in a group of 1549 people with diabetes who attended a screening programme for diabetic retinopathy [8]. In those over 70 years there was a much higher rate of visual impairment (5.1% vs 1.3%) and acuity blindness (WHO 1.2% vs 0.3%, UK 0.6% vs 0.2%) compared to those younger than 70.

In the over-60 age group the most common causes of subnormal vision (log MAR $\geq$0.3 equivalent to Snellen $\leq$6/12 or $\leq$20/40) were cataract, AMD, diabetic macular edema, amblyopia, and glaucoma.

In 2013, the Royal National Institute for the Blind (RNIB) in the UK published an evidence-based review

Box 9.1 Global impact of impaired vision

- 285 million people are estimated to be visually impaired worldwide: 39 million are blind and 246 million have low vision.
- About 90% of the world's visually impaired live in low-income settings.
- 82% of people living with blindness are aged 50 and above.
- Globally, uncorrected refractive errors are the main cause of moderate and severe visual impairment; cataracts remain the leading cause of blindness in middle- and low-income countries.
- The number of people visually impaired from infectious diseases has reduced in the last 20 years according to global estimates work.
- 80% of all visual impairment can be prevented or cured.

Box 9.2 Impact of Visual Loss in the UK

- Almost two million people in the UK are living with sight loss that has a significant impact on their daily lives.
- The leading causes of sight loss in the UK are uncorrected refractive error, age-related macular degeneration, cataract, glaucoma, and diabetic retinopathy.
- The older you are, the greater your risk of sight loss.
- According to figures from Census 2011, there are now over 14.2 million people aged over 60 years in the UK.
- One out of every nine people in the UK aged 60 and over is living with sight loss.
- The fastest growing age group in the UK is 85 years and over. The number of people aged 85 and over has more than doubled over the last 25 years, and by 2035 it is projected to more than double again. Census 2011 indicates that there are 1.4 million in the UK in this oldest-old age group.
- Around 1 in 7 people over the age of 65 and 1 in 3 people over the age of 85 in the UK are living with sight loss.

of sight loss and in February 2014 [9] they published another evidence-based review that came to several key conclusions (see Box 9.2).

There is evidence that Ethnic Minority Groups are at greater risk of vision loss. This is particularly true in the development of glaucoma [10] and diabetic eye disease [11]. The white population are more at risk of developing AMD in older age [12].

Smoking is particularly associated with AMD but is also associated with several eye diseases, including nuclear cataract and thyroid eye disease [13]. In AMD there is a strong association between smoking, vision loss, and blindness.

In the USA, the projected increase in cases of early AMD is from 9.1 million in 2010 to 17.8 million in 2050 [14]. The projected increase between 2010 and 2050 in cases of diabetic retinopathy and vision threatening diabetic retinopathy in people over 65 years is expected to be from 2.5 million to 9.9 million, and from 0.5 million to 1.9 million, respectively [15].

An excellent guide for general practitioners in the UK was published in 2014 by the RNIB with support from the Royal College of General Practitioners, the UK Vision Strategy, and the Thomas Pocklington Trust [16]. It advised that visual loss should be considered in the following circumstances:

- stroke (cerbrovascular accident)
- diabetes
- falls
- dual sensory loss
- learning disabilities
- depression
- dementia
- visual hallucinations
- sleep disturbances
- smoking.

With respect to the elderly, stroke is a problem, particularly the hemianopia with visual loss on one side of the visual field, which can cause considerable difficulties in everyday life for an individual.

Depression is known to be associated with type 2 diabetes and visual loss [17, 18]. Sleep apnea is also associated with type 2 diabetes and diabetic retinopathy [19]. Visual hallucinations are not an uncommon accompaniment of deteriorating vision, usually in elderly people. This was first reported by Charles Bonnet and hence the association is often described as the Charles Bonnet syndrome [20]. It is important that it is recognized that this is associated with deteriorating vision because of the alternative diagnoses of delirium, dementia, psychoses, or a drug-related condition. Elderly people are often reluctant to inform people that they are experiencing vivid pattern pictures or people, which can sometimes be quite unpleasant.

The original causes of visual loss discussed in the article by Congdon are divided here into issues primarily in developing countries and issues in all countries.

9.2.1 Issues primarily in developing countries

1 *Infectious causes*

a) *Trachoma*: There are many programs to prevent the disease, including improving access to clean water and decreasing the number of people infected by treatment with antibiotics. The WHO's SAFE strategy recommends [21]:

- **s**urgery for trichiasis (in growing eyelashes)
- **a**ntibiotic (azithromycin) treatment
- **f**acial cleanliness
- **e**nvironmental improvements

b) *River blindness (onchocerciasis)*: Vector control involves killing the larvae of black fly vectors

using environmentally safe insecticides. The treatment for onchocerciasis is ivermectin. The manufacturer of ivermectin (Merck & Co., Inc.) has provided the drug free of charge since 1987.

c) *Cytomegalovirus in human immunodeficiency*: This cause of visual loss is linked to the control and treatment of the human immunodeficiency virus (HIV). Fortunately this cause has been decreasing with increasing use of antiretroviral therapy.

2 *Vitamin A deficiency*: This tends to affect children and pregnant women in poorer countries. The mortality rate is very high in children who have lost vision from vitamin A deficiency.

3 *Trauma*: Ocular trauma and corneal ulceration are serious public health problems that occur in epidemic proportions in the developing world [22, 23]. In countries that have better road safety and safety at work legislation this is not such a major cause of loss of vision.

9.2.2 Issues in all countries

4 *Refractive error*: One might consider that this would be more of a problem in the developing world but refractive error is a problem in all countries, particularly in the elderly. An article by Taylor in 2005 reporting on vision loss in Australia found that 62% of low vision in 8376 community and 533 nursing home residents was caused by refractive error [24]. The reasons why elderly people may not have their refractive errors corrected may be financial, or be linked to dementia or living in isolation or in nursing homes where access to sight testing is often not routine.

5 *Cataract*: Although cataract is an important cause of visual loss in the elderly, it is a condition that is eminently treatable with removal of cataract and intraocular lens replacement, providing a high standard of cataract surgery is undertaken in a suitable environment. It continues to be an issue in the developing world due to cost, lack of population awareness, shortage of trained personnel, and poor surgical outcomes in some units [25].

6 *Glaucoma*: Glaucoma [26] describes a group of ocular disorders with multifactorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy. Glaucoma is the third most common cause of blindness and is responsible for 10% of blindness worldwide. The condition can be divided into open-angle glaucoma, which is symptomless until an advanced stage of the disease, when a field defect might be noticed by the individual, and closed-angle glaucoma, which presents acutely. Closed-angle glaucoma presents with a red painful eye often associated with nausea and vomiting, which is caused by an anatomical obstruction to the outflow of fluid in the angle of the anterior chamber with a consequent acute rise in intraocular pressure.

Open-angle glaucoma accounts for 90% of glaucoma cases and closed-angled glaucoma for approximately 10% in predominantly white Caucasian populations like the UK and the USA, but angle-closure glaucoma can account for up to 50% of glaucoma cases in populations of East Asian origin [27].

In developed countries, eye drops are commonly used to control intraocular pressure in chronic open-angle glaucoma and a small percentage of patients with open-angle glaucoma require drainage surgery (e.g., trabeculectomy). However, eye drops often need to be administered every day for life, which can prove difficult in poor countries where eye drops are often either not available or very expensive. Hence, surgery is the main treatment for glaucoma in the developing world. In open-angle glaucoma visual loss often affects the peripheral vision before involvement of the central visual field, although blind spots just off-center are also common.

7 *Age-related macular degeneration*: The macula is a critical area of the central retina where there is a concentration of cones that provides the clarity of central vision. Degeneration in the macular area is a common form of visual loss in the elderly. Macular degeneration is generally divided into the "dry" form and the "wet" form. In dry macular degeneration there is a build-up of drusen and the retinal pigment epithelial changes in the macular area with a gradual reduction in vision, usually over several years. Some individuals notice a distortion of vision. Drusen is a build-up of yellow deposits of extracellular material on Bruch's membrane. The retinal pigment epithelium is a layer of cells behind the rods and cone. When there are degenerative changes in the cones in macular degeneration, changes in the retinal pigment epithelial layer become apparent.

In wet macular degeneration choroidal blood vessels come through degenerative areas of Bruch's membrane and leak fluid or blood in the more

superficial layers of the macular area, causing symptoms of distortion and blurring that are more acute and progress over a few days. Diagnostic tests such as fluorescein angiography and optical coherence tomography are helpful in confirming the diagnosis. Until recently there was no treatment for wet macular degeneration and the visual loss depended on the size of the scar forming in the macular area. However, intravitreal injections of vascular endothelial growth factor (VEG F) inhibitors have improved the visual prognosis of this condition in developed countries. The treatment is expensive and is therefore not in widespread use in the developing world. Although VEG F inhibitors do not provide a cure because they work by reducing the leakage and consequent scarring in the macular area, they do appear to reduce the incidence of blindness in areas where they are in widespread use [28].

Risk factors for development of AMD are smoking, high blood pressure, and a family history.

8 *Diabetic retinopathy*: Diabetic retinopathy causes sight loss in one of two ways: by complications of progression of proliferative diabetic retinopathy or by leakage or ischemia in the macular area causing diabetic maculopathy.

When diabetic retinopathy progresses to proliferative diabetic retinopathy, laser treatment has a high success rate in prevention of visual loss provided it is given at the appropriate time. Screening and monitoring program for diabetic retinopathy, which have been developed in the UK, help to detect the appropriate time to treat the individual.

The Diabetic Retinopathy Study (DRS) recommended prompt treatment in the presence of DRS high-risk characteristics, which reduced the two-year risk of severe visual loss by 50% or more and were defined by [29, 30]:

a) the presence of preretinal or vitreous hemorrhage
b) eyes with neovascularization of the disc (NVD) equaling or exceeding a quarter or a third of the disc area in extent with no hemorrhage
c) Neovascularization elsewhere equaling more than half the disc area with hemorrhage (from the NVE).

If the proliferative retinopathy progresses without or despite treatment, there are risks of visual loss from recurrent vitreous hemorrhage, tractional detachment of the retina, and neovascular glaucoma. In the more advanced stages of the disease a vitrectomy operation may be required.

Diabetic maculopathy can develop with leakage or ischemia in the macular area. The mainstay of treatment for leakage in the macular area used to be laser treatment, but in recent years VEG F inhibitors have been shown to provide an important alternative treatment to reduce loss of vision, particularly where the leakage is in the central macular area.

The Early Treatment Diabetic Retinopathy Study (ETDRS) reported that focal photocoagulation of "clinically significant" diabetic macular edema (CSMO) substantially reduced the risk of visual loss [31]. CSMO is defined as:

- thickening of the retina at or within 500 microns of the center of the macula
- hard exudates at or within 500 microns of the center of the fovea, if associated with thickening of the adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening)
- a zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the center of the macula.

The Diabetic Retinopathy Clinical Research Network reported that intravitreal ranibizumab with prompt or deferred laser is more effective through at least 1 year compared with prompt laser alone for the treatment of diabetic macular oedema involving the central macula [32].

Risk factors for progression of diabetic retinopathy can be divided into modifiable and non-modifiable. The modifiable risk factors for progression of DR include control of blood glucose [33], systemic hypertension [34, 35], and blood lipids [36, 37]. The non-modifiable risk factors for progression of diabetic retinopathy include duration [38] of diabetes, a complex relationship with age [39, 40], genetic predisposition [41], and ethnicity [42].

9.3 Conclusions

Visual loss is a key contributor to poor quality of life, functional loss, and reduced independence in aging populations. Early diagnosis and prompt treatment are essential to preserve visual function and well-being.

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CHAPTER 10
Diabetes foot disease

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KEY MESSAGES

- Diabetic foot disease is a serious and preventable complication of diabetes that is associated with significant morbidity.
- Data from different studies suggest that the lifetime risk of developing a foot complication in individuals with diabetes is between 15% and 25%.
- The general principles of foot management apply to older people, but careful attention must be paid to the complex needs of these individuals.
- In managing diabetic foot ulcers, it is essential to screen for the presence of neuropathy.
- Education, medical and surgical treatment, and novel therapies are all available to manage diabetes foot disease in older people.
- There is a greater need for education of carers and health professionals around the complex needs of the elderly.
- Future research must focus around care models that improve outcomes in this age group while preserving quality of life.

10.1 Introduction

Diabetic foot disease is a serious complication of diabetes and is associated with significant morbidity. Data from different studies suggest that the lifetime risk of developing a foot complication in individuals with diabetes is between 15% and 25% [1, 2]. Diabetes is the most common cause of non-traumatic lower limb amputations. Diabetic foot ulcers precede amputations in over 80% of the patients and the likelihood of having a second amputation is nearly doubled in patients with diabetes compared to those without diabetes. Amputation rates are up to 15% greater in patients with diabetes and nearly 20% of all hospital admissions in patients with diabetes are due to diabetic foot ulcers [3]. Diabetic foot disease is also associated with a high risk of mortality, with nearly 50% of those with a diabetes foot ulcer and 70% of those who have had an amputation dying within 5 years. In the UK there are an estimated 100 amputations performed each week in patients with diabetes [4]. Management of diabetic foot disease is associated with significant costs. Data from the USA show that the cost of treating a foot ulcer over a period of 2 years is approximately $28,000 and that of amputation is up to $35,000 [5, 6]. The annual cost to the NHS in the UK for the management of diabetes-related foot ulcers and amputations is estimated to be approximately £650 million [7]. In addition, there are indirect costs relating to diabetic foot disease. Patients with foot ulcers related to diabetes have a prolonged hospital stay and generally poorer outcomes and quality of life.

A significant proportion of foot ulcers is preventable with good quality foot care. However, despite numerous campaigns to increase the awareness of this problem amongst both patients and health professionals, it is concerning that that the number of diabetes-related amputations is on the increase [1].

Diabetes in Old Age, Fourth Edition. Edited by Alan J. Sinclair, Trisha Dunning, Leocadio Rodríguez Mañas, and Medha Munshi.

10.2 Foot disease in older people

In recent years there has been a dramatic increase in the number of people affected by diabetes. Although increases are seen in almost all age groups, the number of older people affected with diabetes has increased markedly primarily due to increased life expectancy in people with diabetes as well as those who are diagnosed later in life. Metabolic risk factors in the elderly are no different to those seen in younger individuals. However, the elderly have a greater burden of other co-morbidities, are more likely to be treated with multiple medications, are less able to self-care, and are more susceptible to hypoglycemia [8]. Elderly patients are also more prone to falls and injuries, and may have significant visual impairment. Aging is associated with vascular disease and a good proportion of elderly patients have vascular disease, the presence of which can adversely affect the outcomes in those with foot ulcers. While the general principles of foot management apply to the elderly, careful attention must be paid to the complex needs of these individuals [9].

10.3 Risk factors for foot disease

Diabetic foot disease is often a consequence of three main factors: poor circulation, diabetic neuropathy, and trauma, often complicated by infection [10, 11]. These factors often coexist and a careful assessment of each of them is essential for good management of diabetic foot disease [3].

10.4 Diabetic neuropathy

Diabetic neuropathy is one of the major risk factors for the development of foot ulcers. Neuropathy is present in over half of patients with diabetes and up to 80% of those with foot ulcers [12]. The risk of neuropathy increases with duration of diabetes. Prolonged exposure to hyperglycemia is a major risk factor for the development of neuropathy. The mechanisms by which hyperglycemia causes microvascular complications is complex and involves several pathways [13]. These include increased flux of glucose and other sugars through the polyol pathway, intracellular accumulation of advanced glycation end products, increased expression of the receptor for advanced glycation end (AGE) products and its ligands, and activation of protein kinase C and hexosamine pathways. In addition to these, vascular compromise resulting from the occlusion of the vasa nervosum is thought to contribute to the development of neuropathy [14].

Typically, patients with foot disease have many years of neuropathy before the more serious signs are manifest. All forms of diabetic neuropathy (peripheral sensory, motor, and autonomic) contribute to foot problems and ulceration [14]. Peripheral neuropathy is characterized by gradual loss of protective sensation in the foot, leading to repetitive stress, deformities, and tissue breakdown [14, 15]. Loss of vibration sense is also common in patients with diabetic neuropathy and frequently leads to falls and foot injuries. Such problems are more common in older people, who are prone to falls and injuries [16]. Motor neuropathy affects the small muscles of the foot, leading to altered distribution of pressure, callus formation, and foot deformities, which in turn increase the risk of ulceration. Loss of foot architecture and varus and valgus deformities are frequently seen as a consequence of motor neuropathy. A significant proportion of patients also have autonomic neuropathy, which is associated with loss of sympathetic tone, local vascular disturbances, decreased sweating, and dry skin, predisposing to ulceration and infection.

Depending on the predominant pathology, ulcers can be classified as neuropathic, ischemic or neuroischemic. Neuropathic ulcers are generally painless, round, surrounded by callus, and located over prominent bony areas of the toes or plantar surface of the foot. The most common sites of ulceration are the first metatarsal head and the plantar aspect of the great toe. Ischemic ulcers, on the other hand, are seen on the lateral aspects of the foot and tend to have irregular margins.

10.5 Charcot's neuropathy

Charcot's neuropathy was originally described in patients with tertiary syphilis but diabetes is now the leading cause of this condition [17]. Over 80% of those who develop Charcot's neuropathy have a duration of diabetes longer than 10 years [18]. Pathogenesis of Charcot's neuropathy is characterized by severe autonomic dysfunction. Arteriovenous shunting leads to increased osteoclastic activity, bone turnover, and destruction. Clinical presentation is often sudden and may be preceded by trivial trauma followed by rapid swelling of the foot. It is important to consider the diagnosis of Charcot's disease in

patients with long-standing diabetes as failure to initiate active treatment can result in significant deformities, such as rocker bottom feet. Diagnosis is based on clinical suspicion and plain X-ray of the foot is usually helpful in confirming the diagnosis. Occasionally, it may be necessary to differentiate Charcot's arthropathy from underlying osteomyelitis. In these circumstances MRI and bone scans should be considered to exclude the possibility of deep-seated infections [19].

Management of Charcot's neuropathy is difficult and requires prolonged immobilization, preferably in a total contact cast [17, 20]. The cast should be left in place for at least 1 year to allow inflammation to settle and help bone remodeling. Medical treatment with bisphosphonates has been shown to be effective in reducing inflammation during the acute phase of the disease and is now increasingly used to treat acute Charcot's foot. Patients with established deformities may require corrective surgery. Charcot's foot is a major risk factor for foot ulceration. Neuropathy and the presence of deformities increases the risk of ulceration due to abnormal distribution of pressure and skin break down.

10.6 Peripheral arterial disease

Like neuropathy, peripheral arterial disease (PAD) is a major risk factor for diabetic foot ulcer and is common in patients with diabetes compared to those without diabetes [21]. True prevalence of PAD is difficult to determine given that many patients do not report any symptoms at early stages and due to the various methods of assessment used to detect it [22]. Nevertheless, using the ankle brachial pressure index (ABPI) as an objective tool, it is estimated that PAD is present in up to 17% of people with diabetes [23]. The presence of PAD is indicative of widespread vascular disease and an active effort should be made to identify other risk factors for vascular disease and treat them appropriately [24].

Although PAD can occur on its own, it is common to find ischemia associated with neuropathy, and it is the combination of ischemia and neuropathy that is associated with significant foot ulceration. Over 50% of people with foot ulcers have significant PAD and this figure is higher in older individuals, where it can be present in up to 70% [12].

Several factors contribute to the development of PAD in diabetes. Chronic exposure to hyperglycemia plays a central role in its development. The steady relationship between the degree of hyperglycemia and risk of PAD was demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS), where every 1% increase in HbA1c was associated with a 28% excess risk of PAD after 18 years [25]. Pathogenesis of PAD in individuals with diabetes has also been linked to other risk factors, such as insulin resistance, coexisting lipid abnormalities, hypertension, and vascular stress resulting from endothelial dysfunction [22]. Additionally, smoking is a well-recognized risk factor for PAD and the relationship between smoking and diabetes persists in patients with diabetes [26]. The presence of PAD often signifies the presence of more widespread vascular disease and other risk factors must therefore be sought and managed actively.

Differences in the pattern of distribution of PAD have been observed in many studies. PAD in diabetes is typically symmetrical and has a femoro-popliteal distribution [21, 27]. Distal arteries are more commonly affected in diabetes whereas the distribution is more proximal in those without diabetes. In addition to the macrocirculation, microcirculation is also affected in diabetes. Disturbances in microcirculation leading to loss of autoregulation and arterio-venous shunting have been noted in patients with diabetes [28].

Symptoms of PAD can be varied and depend on the severity of the disease. In early stages, patients are often asymptomatic but claudication develops in later stages. Rest pain is a characteristic feature of PAD and can be confused with neuropathic pain.

10.7 PAD and foot ulcer healing

The presence of PAD is associated with poor healing of diabetes foot ulcers. Individuals with PAD have significantly lower healing rates, increased risk of amputation, and poorer quality of life outcomes compared to those without PAD [29].

10.8 Other risk factors

Besides neuropathy and PAD, there are other factors that contribute to foot ulceration [11, 15]. These include deformities, reduced mobility of joints, trauma, and metabolic control. The presence of deformities and reduced mobility are commonly associated with neuropathy and, when present, increase the likelihood of injuries and ulcerations. Common deformities of the foot include rear foot varus, fore foot varus, and

Table 10.1 PEDIS classification system for foot ulcers [33].

Grade	Perfusion	Extent	Depth	Infection	Sensation	Score
1	No PAD	Skin intact	Skin intact	None	No loss	0
2	PAD, no CLI	<1 cm^2	Superficial	Surface	Loss	1
3	CLI	1–3 cm^2	Fascia, muscle, tendon	Abscess, fasciitis, septic arthritis		2
4		>3 cm^2	Bone or joint	SIRS		3

PAD, peripheral arterial disease; CLI, critical limb ischemia; SIRS, systemic inflammatory response syndrome.

equinus deformities. Hyperkeratosis leading on to callus formation and ulceration is commonly seen in the presence of these deformities. Ill-fitting footwear increases the risk of ulceration. Tightly fitting shoes, especially with limited space around the toes, and shoes made of non-stretchable material are commonly associated with injuries and ulceration. Assessment of footwear and advice regarding appropriate footwear should be a part of routine foot examinations. Poorly trimmed or ingrown nails are a potential source of infection. Visual impairment is common amongst older patients, who may have difficulty in inspecting their feet and recognizing any injury or infection [30]. These factors can lead to late presentation in the elderly. Help from other members of the family or carers, and frequent foot examination by clinicians can help identify these problems in time and prevent serious ulceration.

10.9 Classification of diabetic foot ulcers

The complex nature of diabetic foot ulcers requires proper assessment of the severity and associated risk factors. Several classification systems have been developed to assist the grading of the ulcers and formulate an appropriate treatment plan. Amongst these, the Wagner classification and the University of Texas systems are commonly used in clinical practice [31]. The Wagner system is one of the oldest classifications and uses a linear grading system with scores ranging from 0 to 5. It takes into account the severity and depth of the ulcer and the extent of gangrene. The Texas system goes further and incorporates a grid system that includes the presence or absence of infection and vascular status in addition to ulcer depth. Comparison of the two systems in one study showed that the Texas system predicted the outcomes better [31]. Other classifications (Kobe and the perfusion extent depth infection sensation (PEDIS)) have also been proposed and offer a different perspective [32, 33]. The PEDIS system was developed by the International Working Group of the Diabetic Foot (IWGDF) for research purposes and classifies the diabetic foot according to five categories: perfusion, extent/size, depth/tissue loss, infection, and sensation, with clear definitions of each sub-category [33] (Table 10.1).

10.10 Assessment of foot at risk

10.10.1 History and physical examination

Assessment of foot at risk must include a detailed history and physical examination. Particular attention must be given to the duration of diabetes, presence of other co-morbidities, and concomitant medication. History must also include any previous ulcerations or amputations and symptoms of claudication. A thorough systemic examination is also warranted as often other co-morbidities, such as vascular disease, may be identified in these patients.

10.10.2 Screening for neuropathy

As diabetic foot ulcers are often associated with significant neuropathy it is essential to screen for the presence of neuropathy. In a clinical setting the simplest test to screen for neuropathy is a 10 g monofilament test. The test involves applying a pressure equivalent to 10 g (the pressure generated by the bending of the nylon monofilament) to different areas on the plantar aspect of foot. The main areas to test are the great toe and base

Table 10.2 Neuropathy disability score sheet [34].

	Score	Right	Left
Vibration perception threshold (normal = able to distinguish vibration at apex of big toe using a 128 Hz tuning fork)	Normal = 0 Abnormal = 1		
Temperature perception on dorsum of the foot (use tuning fork with beaker of ice/warm water)	Normal = 0 Abnormal = 1		
Pin prick (normal = able to distinguish sharp/not sharp when pin applied to big toe)	Normal = 0 Abnormal = 1		
Achilles reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	Total score out of 10		

Maximum score is 10.
A score ≥6 is associated with an increased risk of foot ulceration.

of the first, third, and fifth metatarsals. This test alone, when used on these sites, has a sensitivity of 90% and specificity of 80% for the presence of large fiber neuropathy. Loss of vibration perception is common in diabetes and a predictor of foot ulceration. Vibration sense can be evaluated using a tuning fork as well as through a biothesiometer. Loss of vibration perception by the patient when the examiner can still perceive it is an indication of neuropathy. The biothesiometer is a hand-held device with a rubber factor that is applied to the distal aspect of the toe. A vibration perception threshold of more than 25 V is often considered to be consistent with the loss of vibration sensation and presence of neuropathy. Presence of neuropathy can also be assessed by using the neuropathy disability score, which is a composite score from testing vibration, pin prick, temperature, and Achilles tendon reflex. The maximum score for each foot is 5 and a total score of 6 for both feet combined is predictive of foot ulceration [34] (Table 10.2).

10.10.3 Screening for peripheral vascular disease

Given that half the patients with foot ulcers have significant PAD, it is important to screen patients for the presence of ischemia. Tests used to assess circulation can be broadly grouped into those that provide information on (i) hemodynamic status and (ii) anatomical distribution. The most commonly used screening test for PAD is the ABPI, which is the ratio of systolic blood pressure at the ankle to the systolic blood pressure at brachial artery. An ABPI value of less than 0.9 is highly suggestive of PAD and a value less than 0.6 indicates severe ischemia. An ABPI ratio greater than 1.3 can be seen in older patients and may be due to medial arterial calcification. These results must therefore be interpreted cautiously. While low ABPI values indicate the presence of PAD, higher values do not exclude underlying ischemia. Tissue perfusion can also be assessed by transcutaneous oxygen pressure measurement. Transcutaneous oxygen pressures greater than 50 indicate good tissue perfusion whereas values less than 25 are commonly associated with poor wound healing. As per the recommendations of the IWGDF, patients with an ABPI value >0.6 and tissue oxygen pressures >50 can be managed conservatively without the need for revascularization. Many other novel tests are also used to assess tissue perfusion, including hyper-spectral imaging and skin perfusion pressures measured by Doppler.

Further evaluation of arterial circulation should be undertaken when revascularization is considered. The gold standard for assessing peripheral circulation is digital subtraction angiography [22, 28], but with the advent of newer and more sophisticated radiological techniques this has been superseded by non-invasive techniques such as Doppler ultrasound angiography, CT angiogram, and MR angiogram. The main advantage of digital subtraction angiography over other techniques

is that it can visualize the arterial circulation, and identify and correct stenoses during the same procedure. Digital subtraction angiography may not be suitable in patients with renal impairment and other co-morbidities and is associated with rare but increased complications such as dissection, pseudoaneurysm, and hematoma.

10.11 Principles of management

10.11.1 Prevention

Considering the overall risk of foot ulceration in patients with diabetes and the high recurrence rates in those with previous ulceration, every effort must be made to identify those at risk and prevent ulceration. Education, regular foot checks, and effective control of risk factors can all play a prominent role in preventing serious foot disease [2].

10.11.2 Education

Education around good foot care must be targeted towards both patients and healthcare professionals [2, 35]. Many older patients depend on their carers for their diabetes care and education of carers and relatives must be considered when treating older patients. Educational packages involving lectures, workshops, and telephone reminders have been studied [2]. Although these studies have focused on behavioral change, improvements in knowledge and reduction in ulceration and amputation rates have been reported. Studies evaluating the educational initiatives targeted towards health professionals include computerized reminders and implementation of clinical guidelines for management of foot problems. Improved rates of screening and reduction in the rate of amputations have been reported in these studies, suggesting education of health professionals is highly effective [36, 37].

10.11.3 Annual foot checks

Regular foot examination allows early detection of foot at risk and helps target further investigation and management [38]. Annual foot checks for patients with diabetes are now a part of the annual review process and must include a detailed assessment for the presence of anatomical deformities, skin and nail changes, loss of sensation, and vascular insufficiency. The foot check must also include examination of injuries relating to ill-fitting footwear.

10.12 Treatment of diabetic foot ulcers

Effective management of diabetic foot ulcers requires a multidisciplinary team approach. The team should include a physician, podiatrist, vascular surgeon, orthopedic surgeon, and orthoptist, all of whom have a keen interest in diabetic foot disease. There is strong evidence to suggest that a multidisciplinary team approach has better clinical outcomes and reduces the need for amputation [2, 39].

The main of goal of treatment is to achieve wound closure as soon as possible. The key elements to achieve this are control of infection, assessment and treatment of ischemia, adequate immobilization, and improvement in wound condition.

10.13 Control of infection

Although infection does not directly cause foot ulceration, the presence of infection complicates the ulcer and can interfere with wound healing [40]. Impaired neutrophil response as a consequence of poor glycemic control and the coexistence of neuropathy and PAD increase the likelihood of infection in individuals with diabetes [41, 42]. Infection can be fairly localized and superficial, spreading (cellulitis), or deep-seated (osteomyelitis). The diagnosis of infection in patients with a foot ulcer is mainly clinical. Infection should be suspected in the presence of systemic symptoms such as fever, chills, and elevated leucocyte count. Other signs pointing to infection include purulent discharge and a change in the odor of secretions. While superficial infections may be evident on inspection, deep-seated infections need careful examination and probing. Around 50–60% of ulcers are complicated by osteomyelitis [43] and the positive predictive value of probing to bone in order to detect underlying osteomyelitis is reported to be around 90% [44]. In cases where osteomyelitis is suspected, radiological investigations using plain radiographs can provide additional information. Evidence of bone destruction seen on plain radiographs is suggestive of osteomyelitis. More recently, MRI of the foot has emerged as a preferred investigation for the diagnosis of osteomyelitis and to determine the extent of soft-tissue infection [43]. Other investigations, such as white cell scan, are of value when MRI is contraindicated.

Most chronic ulcers are polymicrobial. Nevertheless, establishing the microbiology of the ulcers is useful for appropriate management [39]. Superficial wound swabs are of limited utility given the polymicrobial nature of the wounds, and commonly yield mixed growth and contaminants. On the other hand, deep-tissue specimens obtained using curettage and scraping of the base of the ulcer are useful in establishing the cause of infection. *Staphylococcus aureus* is the most common organism associated with diabetic foot ulcer followed by β-hemolytic streptococci. Other common pathogens include Gram-negative cocci, pseudomonas, and anaerobes (often seen in mixed infections) [43].

Treatment of an infected diabetic foot involves prompt initiation of antibiotic treatment. Infections progress rapidly in patients with diabetes and failure to control the infection can lead to serious limb-threatening or life-threatening situations. There are three main considerations involving antibiotic treatment: the choice of antibiotic, the route of administration, and the duration of treatment [40, 45–47]. Empirical treatment with a broad -spectrum antibiotic that covers *Staphylococcus aureus* and β-hemolytic streptococci is recommended as an initial choice. Subsequently, antibiotic choice can be tailored depending on the response and a more definitive identification of the causative organism.

For most superficial infections, oral antibiotic treatment with broad coverage would be sufficient. Intravenous treatment must be considered in patients who are systemically unwell, those who are suspected to have deep-seated infections, and those who are unlikely to comply with offloading. There is very little evidence to determine the appropriate duration of antibiotic treatment and duration of treatment is mainly based on the severity of infections. Recommended duration for antibiotic treatment is 1–2 weeks for superficial infections, 2–3 weeks for severe infections, and up to 6 weeks for osteomyelitis [45, 48].

10.14 Improvement in wound condition

10.14.1 Debridement

Good preparation of the wound bed is important to facilitate wound closure. Debridement is an essential component of wound preparation and involves removal of dead tissue and foreign material, which in turn encourages healing by reducing pressure and stimulating local growth factors [49, 50]. It is widely perceived that debridement improves ulcer healing and it is therefore practiced by most clinicians treating chronic ulcers [50]. Debridement can be broadly classified as surgical and non-surgical. Surgical debridement refers to removal of callus and necrotic tissue using a sharp scalpel. Regular debridement (weekly) has been shown to significantly reduce healing times compared to less frequent debridement and much lower ulcer recurrence rates [51]. Additionally, regular debridement in conjunction with measures to reduce edema have been associated with much better outcomes. Sharp debridement, however, requires a certain level of practitioner expertise and training, and is best undertaken within a multidisciplinary setting [49].

More recently, a lot of interest has been generated in non-surgical methods of debridement. Non-surgical methods include mechanical (high-pressure irrigation), autolytic (a natural process occurring in a moist environment), enzymatic (enzymatic digestion of the necrotic tissue, e.g. Streptokinase), and biological (maggot debridement treatment, MDT) [3]. These techniques offer specific advantages, especially where surgical debridement may not be ideal. Autolytic treatments using hydrogels have been compared with standard wound care and shown to have some benefits in promoting ulcer healing [52]. MDT, also known commonly as larval therapy, involves application of the sterile larvae of the green bottle fly (*Lucilia sericata*) to the wound. These larvae are known to stimulate the healing process through secretion of autolytic enzymes that digest the necrotic tissue while sparing healthy granulation tissue. Improvements in ulcer healing and reduction in antibiotic treatment days have been reported in some studies with this treatment [53, 54]. This treatment is, however, expensive and may not be preferred by many patients.

Despite its perceived benefits, the value of debridement in ulcer healing has not been convincingly established. A recent Cochrane review that examined the benefits of debridement versus standard care concluded that the benefits of debridement could not be confirmed mainly due to the fact that most trials were small, had poor methodology, and were not replicated [52, 55].

10.14.2 Dressings

The availability of varied dressings has revolutionized the management of diabetic foot ulcers [3]. These include hydrogels, foams, films, hydrocolloids, and alginates. Based on their characteristics they can be broadly classed as passive and active. Passive dressings are primarily used for wound protection and absorption of exudates. Active dressings maintain a moist environment and encourage wound healing through stimulation of growth factors and preventing microbial growth. No dressing is perfect and the choice of dressing is determined by the wound depth and location, presence of exudates, and condition of wound margins. Hydrogels have been studied in many clinical trials and have been shown to improve wound healing when compared to standard care. These benefits must be weighed against the high cost of some of these products.

10.14.3 Pressure modulation

Pressure modulation, or offloading, is an essential component of the management of diabetic foot ulcer. The main objective of offloading is to redistribute the pressure to all areas of the foot and thereby encourage ulcer healing [3, 56]. Traditional methods of pressure modulation include bed rest, use of crutches and wheel chairs, customized splints, and total contact casts (TCCs). The choice of treatment is determined by other factors such as likelihood of compliance with the treatment and the presence of infection. Consideration of individual circumstances, especially in the elderly, is important before deciding on the technique used for offloading. Amongst the several techniques used, the most effective option is the TCC. TCCs were first described in patients with Hansen's disease in the early 1930s but were later used to treat chronic ulcers from other conditions, including diabetes. The TCC is considered the gold standard treatment for offloading and involves the application of light padding and a plaster cast [57]. The effectiveness of this technique is proven in several clinical trials. Compared to standard treatment TCC has been shown to reduce the time for ulcer healing. TCC, when used before debridement, has also been shown to be superior to using debridement alone. Despite its effectiveness, there are several limitations associated with TCC. Application of TCC requires a certain degree of skill and training, and if done incorrectly can cause skin irritation and ulceration. However, the main disadvantage of this technique is that it does not allow self-inspection of wounds and administration of any topical treatments. Moreover, many patients perceive TCC to be inconvenient in conducting daily activities such as bathing and sleeping, leading to poor acceptance of it. TCC must not be used in the presence of active infection or osteomyelitis, and is contraindicated in the presence of infection.

Alternative methods of pressure modulation that have been used include removable cast walkers (RCWs) and instant TCC (iTCC). RCWs have the advantage that the offloading device can be removed during bathing and sleeping. As it can easily be removed it also allows regular self-inspection of the wounds. However, the effectiveness of this technique is poor compared to TCCs and reported ulcer healing times are longer in patients treated with RCWs when compared to those treated with TCCs. RCWs do not achieve the extent of immobilization seen with TCCs and this is one of the reasons why the healing rates do not match that of TCCs.

More recently, iTCC has emerged as a technique that combines the convenience of RCWs and the effectiveness of TCCs. iTCCs involve wrapping a RCW with a single layer of bandage or casting tape. The bandage enforces immobilization while the RCW allows wound inspection and local treatment. This technique has been shown to be as effective as TCCs and superior to RCWs alone in many clinical trials. iTCCs are also easy to apply and require less time, skill, and costs compared to TCCs. Because of these multiple advantages, iTCC is expected to emerge as the gold standard technique for offloading.

10.14.4 Revascularization

Although there is not much evidence to show that revascularization prevents foot ulcers, the presence of ischemia can adversely influence the outcomes and is associated with delayed healing of ulcers. It is therefore important to identify and treat ischemia in patients with diabetic foot ulcers.

Ischemia can be managed conservatively with medical management. Revascularization is indicated in the presence of disabling claudication or critical limb ischemia. Critical limb ischemia must always be treated with urgency as failure to correct ischemia is invariably associated with limb loss. Urgent referral to a vascular surgeon for consideration of revascularization is indicated in these situations.

Revascularization procedures can be endovascular or open. Endovascular procedures are less invasive and are most effective when the lesions are focal and involve proximal arteries. With better instrumentation and experience they have recently been shown to be effective even when there is involvement of distal arteries. Data from the USA shows that there was a five-fold increase in the number of endovascular procedures performed over a 20 years period between 1980 and 2000. Despite their popularity, re-stenosis after endovascular procedures is common and may need regular postoperative follow-up. The use of stents with angioplasty has to some extent minimized this problem but the long-term effectiveness of these combined procedures needs to be established. Endovascular techniques are less successful in patients with diffuse disease (commonly seen in patients with diabetes) and open surgical procedures must be considered in these situations. Open surgical procedures involve bypass to the tibial and pedal vessels using autogenous veins.

Below-knee bypass surgeries account for nearly 75% of all procedures in patients with diabetes and the use of great saphenous veins to perform the bypass is now a preferred option. Compared to endovascular procedures, bypass surgeries offer better durability and are more effective, particularly when the disease is diffuse.

Revascularization may not be feasible in all ischemic limbs and this may be due to lack of a target vessel, irreversible gangrene, or non-availability of autogenous veins. In these circumstances amputation should be considered.

10.14.5 Novel therapies

Several novel options for wound management have been developed in recent times and include treatments such as negative pressure wound therapy (NPWT), hyperbaric oxygen, bioengineered skin, and the use of growth factors. NPWT has been evaluated in many clinical trials and has been shown to improve ulcer healing by reducing healing times and ulcer recurrence [58]. In a large study involving 342 patients, NPWT was associated with reduced healing times, smaller ulcer size, and lower rates of amputation [59]. The results from some other studies, however, have been less convincing and suffer from small numbers, poor description of baseline data, and lack of blinding.

Hyperbaric oxygen treatment (HBOT) involves administration of 100% oxygen to patients in multiple daily sessions. HBOT is thought to improve tissue oxygenation and local perfusion, and reduce edema and inflammation. It is also thought to promote healing through fibroblast proliferation and angiogenesis. Both topical and systemic treatment HBOT have been studied. In studies where HBOT has been used systemically, significant improvements in ulcer healing have been reported. A large double randomized trial comparing HBOT with standard care showed better healing rates in the intervention group at 12 months [60]. However, other studies and meta-analysis involving HBOT have not confirmed these benefits. HBOT is time-consuming and very expensive, with a complete course of treatment estimated to cost around $50,000 (Medicare) or $200,000 (privately).

Many different growth factors have been evaluated for treatment of diabetic foot ulcers. Amongst these the use of platelet-derived growth factor (PDGF) has shown the most promise. Clinical trials using PGDF have shown better ulcer healing rates in patients using this treatment compared to standard care. Like all other novel therapies, treatment with PDGF is expensive, which limits its use in clinical practice.

10.15 Surgery

10.15.1 Corrective surgery

Surgery to correct deformities can be useful to relieve plantar pressure and prevent ulceration. Procedures such as Achilles tendon lengthening have been shown to be effective in reducing healing times as well as preventing ulcer recurrence.

10.15.2 Amputation

Amputation is indicated in the presence of life-threatening infection, critical ischemia not amenable to revascularization, and the creation of a functional stump to accommodate foot prosthesis. While the primary goal of foot ulcer management is limb salvation, this may not be possible in all cases. In fact, amputation may offer a better functional outcome than prolonged medical treatment in certain circumstances. In these situations, the decision to amputate must be individualized after careful assessment of co-morbidities, psychological needs, and patient preferences.

10.16 Conclusion

Diabetic foot disease is a serious but potentially preventable complication of diabetes. Following the St Vincent declaration, there have been several advances in our understanding of the pathophysiology this condition. These advances have helped us identify feet at risk and expand our therapeutic options. Regrettably, however, the morbidity and mortality associated with diabetic foot disease continues to be high. Management of diabetic foot disease requires a holistic approach and this is most relevant in the older age groups where the physiological changes associated with aging make the elderly more vulnerable to develop foot ulcers and adversely influence the overall prognosis. This is further complicated by the fact that there has been very little research in older age groups. While the essential principles of footcare apply to older age groups as much as younger people, the benefits of interventions must be carefully assessed against the background of declining functional status, associated co-morbidities, and the inability to self-care. In this context, there is a greater need for education of carers and health professionals around the complex needs of the elderly. Future research must focus around care models that improve outcomes in this age group while preserving the quality of life.

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CHAPTER 11
Diabetes, neuropathy, and old age

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KEY MESSAGES

- Neuropathic complications occur in both younger and older patients with diabetes; the primary difference is older patients have a higher chance of associated morbidity.
- The risk of developing any neuropathic complication increases with age.
- The type of neuropathies seen older patients include a peripheral sensorimotor polyneuropathy, small fiber neuropathy, focal mononeuropathies, radiculoplexus neuropathies, and autonomic neuropathy.
- Regular screening can help identify subclinical neuropathy and will reduce the development of complications.
- The management of any patient with diabetes and neuromuscular complications takes a two-pronged approach: an aim for improved glycemic control and symptom management.

11.1 Introduction

The prevalence of diabetes in elderly populations is almost 12 times that of diabetes in a younger population (<45 years) [1]. The elderly population represents a group of people who have a greater burden of medical and functional limitations, and are more vulnerable to adverse outcomes in the context of diabetes. Any complication of diabetes that potentially affects mobility can have a huge functional impact. An elderly patient with diabetic peripheral neuropathy is at a far greater risk of falling than their younger counterpart [1, 2]. Mortality is more common in older adults with diabetes compared to those without [1]. The relationship between diabetes and disability is magnified by an associated peripheral neuropathy in older diabetic individuals [3]. It is important that physicians who care for older individuals with diabetes are mindful of the risks of medication polypharmacy, functional capacity, and home supports when planning their care. Neuropathic complications occur in both younger and older patients with diabetes; the primary difference is older patients have a higher chance of associated morbidity.

11.2 Frequency of neuropathy development

Although many different subtypes of neuropathy can occur in diabetes, the risk of developing any neuropathic complication will increase with age. Longitudinal studies in type 1 diabetes (the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC)) have shown the prevalence of symptoms and signs of neuropathy increase over time [4]. As people with type 1 diabetes reach older age, the risks of neuropathy continue to increase. For individuals with type 2 diabetes, longitudinal studies show a greater risk of neuropathy development over time compared to individuals with type 1 diabetes. Thus, elderly individuals with either type 1 or type 2 diabetes have high risks of neuropathy

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(despite major differences in diabetes duration). The frequency of neuropathy development by age will be discussed in greater detail for each neuropathy subtype.

11.3 Types of diabetic peripheral neuropathy

The effects of diabetes on the nervous system are widespread and include different underlying pathophysiologies. Diabetic peripheral neuropathies are typically classified according to their anatomical distribution or by their pathophysiology [5]. Manifestations of neuropathies in diabetes include a peripheral sensorimotor polyneuropathy (which is the most common), small fiber neuropathy, focal mononeuropathies (carpal tunnel syndrome being the most common), radiculoplexus neuropathies (lumbosacral being the most common, but include thoracic and cervical subtypes), and autonomic neuropathies.

11.3.1 Diabetic sensorimotor polyneuropathy

A diabetic sensorimotor polyneuropathy (DSPN) is the most common peripheral neuropathy associated with diabetes [6]. It affects patients with both types 1 and 2 diabetes. In people with type 2 diabetes it is not uncommon for this to be present at the time of diagnosis and it is known to occur in the pre-diabetic stage [7]. Neuropathy is not present prior to diagnosis in type 1 diabetes [8]. The typical presentation of DSPN is an insidious symmetric numbness and tingling in the feet that gradually spreads to involve the legs up to the knees. It does not follow a single nerve or dermatomal distribution. The neuropathy development follows a "stocking and glove" pattern and once the symptoms reach the knees the hands may become involved. DSPN is primarily an axonal neuropathy with the longest nerves in the body being affected earliest, thus typically presenting in the toes and progressing to more proximal sites. Approximately a third of patients with DSPN develop pain with the neuropathy and this tends to be more prevalent in type 2 than type 1 diabetes [8]. In DSPN there is damage to both large and small nerve fibers. Large fiber involvement manifests as loss of proprioception, vibratory and light touch sensation. Small fiber neuropathy results in altered sensation of temperature, pin prick, and pain. Small fiber neuropathy is more likely to present with symptoms of neuropathic pain. Neuropathic symptoms tend to be worse at night, while relaxing or trying to sleep. People with neuropathy often report that walking, standing or moving will transiently alleviate neuropathic symptoms. The clinical examination typically reveals a length-dependent pattern of sensory loss of both large and small fiber function. In some individuals the sensory loss will be apparent on the clinical examination prior to the development of symptoms [9–11].

Due to the insidious nature of neuropathy progression, risks of painless injuries to the feet need to be monitored closely in individuals with diabetes. Sensation loss is a major risk factor for limb fractures, plantar ulcers, and neurogenic arthropathy so periodic assessment of foot sensation independent of the presence of symptoms should be carried out. The 10 g monofilament is often used to detect loss of protective sensation in individuals with diabetes [12]. The 10 g monofilament should not be used as a screening tool for mild to moderate neuropathy because neuropathy is often present for years before it is of sufficient severity to be noted by loss of the 10 g monofilament sensation [13].

Weakness in regions of neuropathy is not a prominent feature of DSPN except in very advanced cases, but when present will also be in a length-dependent pattern. Weakness will manifest first with atrophy of the intrinsic foot muscles, resulting in hammer toes and fallen foot arches. In older people with diabetes the presence of a DSPN can have a significant functional impact. There is a greater incidence of falls in people with DSPN secondary to a combination of loss of balance, diminished distal sensation, and distal weakness. Fall prevention is of paramount importance in an older patient population as falls result in hip fractures and other injuries that lead to prolonged periods of rehabilitation [2, 3].

11.3.2 Focal mononeuropathies

In addition to a distal symmetric polyneuropathy, people with diabetes are also at increased risk for the development of mononeuropathies (the injury of a single nerve) at common compression sites, including the median nerve at the wrist (carpal tunnel syndrome), ulnar neuropathy at the elbow, peroneal neuropathy at the fibular neck, lateral femoral cutaneous neuropathy, and tarsal tunnel syndrome. The exact reason for this

increased susceptibility is likely multifactorial [14]. It has been postulated that nerves in people with diabetes are more susceptible to entrapment and perhaps personal cofactors such as repetitive activities or obesity could produce focal nerve injury at points of increased vulnerability and produce symptoms more easily in people with diabetes [15]. The increased prevalence may be related to repeated undetected trauma, metabolic changes or accumulation of fluid and edema within the confined space where the entrapment occurs [16].

The prevalence of carpal tunnel syndrome in people with diabetes varies in the literature and ranges from 8.7% to 19.4% for symptomatic carpal tunnel syndrome and from 22% to 29% for asymptomatic carpal tunnel syndrome [17]. The difference in prevalence (between symptomatic and asymptomatic) may be related to a decrease in awareness of symptoms in individuals with diabetes resulting in more advanced nerve pathology prior to the presentation of clinical symptoms. Due to the increasing prevalence of diabetes with age, focal mononeuropathies will be commonly seen in the elderly.

Other entrapment neuropathies that occur with a higher prevalence in people with diabetes include ulnar neuropathy at the elbow, peroneal neuropathy at the fibular head, lateral femoral cutaneous neuropathy, and tarsal tunnel syndrome. Tarsal tunnel syndrome is a painful lower limb entrapment that may be confused with distal symmetric polyneuropathy. Tarsal tunnel syndrome occurs when the tibial nerve becomes trapped in the space that lies between the medial malleolus and calcaneus. Foot pain may be severe, burning and worse on standing or walking. A Tinel sign (symptoms upon percussion of the nerve) on the underside of the medial malleolus is frequently noted. A diagnosis of tarsal tunnel syndrome becomes more difficult with a coexistent DSPN. When the neuropathy is severe the diagnosis of tarsal tunnel syndrome may be impossible [18].

Another common entrapment neuropathy in people with diabetes is compression of the lateral femoral cutaneous nerve (meralgia paresthetica) as it passes under the inguinal ligament. Lateral femoral neuropathies result in pain, paresthesia, and sensory loss in the lateral aspect of the thigh. Diabetes and age both independently increase the risk of developing lateral femoral cutaneous nerve syndrome [19]. Temporary symptomatic management is routine, although a minority of individuals may require long-term symptomatic therapy.

Cranial mononeuropathies occur in diabetes at a higher rate than in the general population. The nerves most commonly involved include cranial nerves III, IV, VI, and VII [18]. The underlying pathophysiology in cranial mononeuroapthies, in contrast to the entrapment neuropathies, appears to be vasculitis with ischemia and subsequent nerve infarction. Onset is typically acute and associated with pain. The pain generally resolves with the development of diplopia. The clinical course of cranial mononeuropathies tends to be self-limited with spontaneous resolution over weeks to months. This recovery is in contrast to the entrapment neuropathies, which have an insidious onset with progression that tends to persist without intervention. A mononeuropathy of the oculomotor nerve appears to be the most common cranial mononeuropathy in diabetes [20]. Involvement of the pupil has been used as a clinical sign to distinguish between an ischemic third nerve palsy (less commonly involving the pupil) and a posterior communicating aneurysm compressing the third nerve. An aneurysm causes compression of the parasympathetic fibers, which are present on the outer portion of the nerve, resulting in pupil dilation. However, studies show that pupillary involvement can occur in up to 25% of ischemic third nerve palsies [21], therefore imaging is still recommended upon development of a focal mononeuropathy. Facial (seventh) nerve palsies are common in the general population and it is unclear if their overall incidence is higher in the context of diabetes mellitus.

11.3.3 Radiculoplexus neuropathy

Radiculoplexus neuropathy is another form of diabetic peripheral neuropathy. It typically involves the lumbosacral region (also referred to as diabetic amyotrophy or diabetic lumbosacral radiculoplexus neuropathy, DLPRN), but both thoracic and cervical segmental involvement have been described [9]. It classically begins in the distribution of the femoral nerve. Upper extremity involvement typically presents as a unilateral or asymmetrical sensorimotor neuropathy that primarily affects the hands and forearms. One smaller series reported arm involvement in 15% of cases [22]. In a larger series of 105 patients there was upper limb involvement in 15 of the 105 cases [23]. The neuropathy is typically subacute in onset and associated with pain. The pain can be severe and quite persistent, interferes with activities of daily living, and can require hospitalization. It begins asymmetrically and tends to

involve proximal more frequently than distal muscles. As the pain subsides the weakness becomes more apparent. Sensory and autonomic fibers may be involved. Approximately half of patients experience some symptoms of autonomic disturbance. Commonly, there is significant weight loss associated with this form of diabetic neuropathy. While the radiculoplexus neuropathy begins asymmetrically it spreads to involve the contralateral limb in a majority of cases. Patients can develop new regional signs for many months to years before a steady state is reached. It can result in moderate to severe disability. The median age of onset is early to mid-60s and the majority of affected individuals have type 2 diabetes [24–27]. Radiculoplexus neuropathy occurs most commonly in individuals with good glycemic control and relatively recent diagnosis of diabetes, who are on both oral hypoglycemic agents and insulin, and who have a low rate of microvascular complications. The natural history is a gradual but incomplete improvement. Pain is usually the first symptom to improve and often does to the largest degree. There are reports in the literature of a painless variant of this neuropathy. The painless syndrome has some noticeable differences. It tends to begin insidiously and progresses at a slower pace. There tends to be more severe distal segment impairment and upper limb impairment. Both, however, are associated with autonomic and sensory involvement [28].

The responsible pathologic abnormalities are multifocal and in roots, segmental nerves, lumbar or lumbosacral plexus, and peripheral nerves. The pathophysiology is thought to be ischemia from microvasculitis. This hypothesis explains both the axonal degeneration and segmental demyelination observed on biopsy specimens. It is thought that diabetes predisposes patients to altered immunity, leading to an autoimmune attack on the nerve small blood vessels [26, 29]. Due to the age of onset, the frequent involvement of the lower extremities, and the incomplete resolution of the symptoms, many older people will require ambulatory aids and will have significant morbidity. Management of pain often requires polypharmacy and adds further risks to older individuals.

11.3.4 Chronic inflammatory demyelinating polyneuropathy in diabetes mellitus

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated inflammatory disorder of the peripheral nervous system. It typically presents with chronic progressive, stepwise progressive or relapsing weakness. It affects both distal and proximal muscles. Occasionally it can involve muscles in the face but it tends to spare the extraocular muscles. Sensory symptoms include numbness, tingling, gait imbalance, and occasionally painful paresthesia [30, 31]. There are conflicting reports in the literature about whether the frequency of CIDP is increased in individuals with diabetes [32, 33]. Identifying CIDP in patients with diabetes can be difficult because there are many different neuropathies that occur in association with diabetes. Both distal symmetric polyneuropathies and radiculoplexus neuropathies are known to have some demyelinating features on nerve conduction studies (NCSs) and they may be confused with CIDP in people with diabetes [34]. One study compared patients with a demyelinating form of distal symmetric polyneuropathy to patients with diabetes who were diagnosed with CIDP [35]. They found that patients with CIDP and diabetes were older, and had a shorter duration of diabetes, better glycemic control, and more severe nerve injury than patients with a demyelinating form of distal symmetric polyneuropathy. CIDP should be kept in the differential diagnosis of diabetic patients with subacutely progressive neuropathies and motor involvement. The presence of pain and multifocal asymmetric weakness may help in the diagnosis of a radiculoplexus neuropathy, but a painless variant of this has been described, contributing to potential ambiguity in the diagnosis [28]. An accurate diagnosis is of utmost importance in CIDP because it is an immune-mediated neuropathy that is responsive to treatment [36]. One study reports that patients with diabetes and CIDP respond to immunotherapy at a similar level to patients with CIDP alone. The only factor that seemed to affect treatment outcome was the duration of the neuropathy and not the presence of diabetes. There is little data on the prevalence and different features of CIDP specifically in an elderly population. Gorson *et al.* looked at the influence of diabetes mellitus on CIDP. Their patient cohort were older and they noted that except for a higher frequency of imbalance the clinical features were indistinguishable from those with idiopathic CIDP [37].

11.3.5 Diabetic autonomic neuropathy

Autonomic abnormalities can occur in diabetes mellitus with or without the presence of a large fiber neuropathy. Autonomic dysfunction can affect cardiovascular,

genitourinary or gastrointestinal systems, causing a wide variety of symptoms. Individuals with diabetic autonomic neuropathy can develop orthostatic hypotension, resting tachycardia, tachyarrhythmias, gastroparesis, impotence, and bladder dysfunction [38, 39]. Changes in sudomotor (sweat) function often occur with a loss of thermoregulatory sweating in a length-dependent distribution that can progress to the upper parts of the limbs. In extremely advanced cases this can result in global anhidrosis. In some cases, individuals with diabetic autonomic neuropathy may present with hyperhidrosis (increased sweating). The hyperhidrosis occurs in more proximal regions and is often a compensatory thermoregulatory mechanism because of the distal anhidrosis. Individuals may present with excessive sweating in the trunk, face, and scalp as their primary complaint [40]. Sudomotor dysfunction can lead to distal cracking and fissuring of skin (typically in the feet), which serves as an environment for microorganisms to enter, increasing the risk of infection.

One of the most common and debilitating complications of diabetic autonomic neuropathy is gastroparesis. This is a motility disorder involving delayed gastric emptying with no evidence of physical obstruction. Although the severity of gastroparesis can fluctuate with glycemic control, gastric emptying largely depends on vagal nerve function, which can be severely disrupted in diabetes. Symptoms include early satiety, nausea and vomiting, bloating, and abdominal pain. Gastroparesis can have a significant impact on quality of life [41]. Fluctuation in food transit results in unpredictable oscillation in blood glucose levels and increases the time required for absorption of food and medicines [42]. It can result in a higher rate of hospitalization.

The genitourinary system has significant autonomic innervation and can be affected in diabetic autonomic neuropathy. The earliest manifestation of autonomic dysfunction in the bladder is impaired bladder sensation, an elevated threshold for initiating the micturition reflex, and an asymptomatic increase in bladder capacity and retention. When there is damage to the efferent parasympathetic fibers to the urinary bladder, symptoms such as hesitancy in micturition, weak stream, and dribbling occur, with a reduction in detrusor activity. This leads to incomplete bladder emptying, an increased post-voidal residual, decreased peak urinary flow rate, bladder over-distension, and urine retention [43]. Finally, overflow incontinence occurs because of denervation of the external and internal sphincter [10, 43]. Diabetic autonomic neuropathy is also associated with erectile dysfunction. Erectile dysfunction may be the presenting symptom of diabetes, and more than 50% of men with type 2 diabetes report the onset of erectile dysfunction within 10 years of diagnosis [38]. In men, neuropathy can cause loss of penile erection, retrograde ejaculation or both. Morning erections are lost and impotence progresses over a period of 6 months to 2 years. Autonomic neuropathy contributes to erectile dysfunction by impeding the cholinergic activation of the erectile vasodilation. Associated vascular endothelial dysfunction is another contributing factor to erectile dysfunction. The close association between erectile and endothelial dysfunction stresses the increased risk for development of generalized vascular and cardiovascular disease. All diabetic patients with erectile dysfunction should undergo a thorough cardiovascular evaluation [38].

Cardiovascular autonomic neuropathy in diabetes is a debilitating complication. The duration of diabetes and history of poor glycemic control are independent risk factors for developing cardiovascular autonomic neuropathy irrespective of type of diabetes [43, 44]. Cardiovascular autonomic neuropathy is a manifestation of a length dependent neuropathy. The vagus nerve is the longest nerve of the autonomic nervous system and controls cardiovascular parasympathetic function. The initial manifestation of a cardiac autonomic neuropathy in diabetes may be a resting tachycardia. The reduction of parasympathetic function leads to a sympathetic predominance. With disease progression, this translates to diminished heart rate variability to deep breathing. Other complications of cardiovascular autonomic neuropathy include diminished control of blood pressure, heart rate, and stroke volume in response to exercise. Orthostatic hypotension occurs in more advanced cases of cardiovascular autonomic neuropathy and is associated with sympathetic denervation. There is an impaired sympathetic response to postural change, with an inadequate heart rate response and diminished peripheral vasoconstriction resulting in orthostatic hypotension [39, 44]. Several meta-analyses of individuals with diabetes have identified that cardiovascular autonomic neuropathy is associated with a large increase in mortality, particularly in older patients. Although cardiac autonomic neuropathy may not directly cause the increase in mortality, it does highlight

the individuals that are at risk. Mortality rates of approximately 30% over 5 years are noted in individuals with impaired cardiovascular autonomic function in the setting of diabetes [39, 44, 45].

11.3.6 Treatment-induced neuropathy in diabetes

This disorder, also referred to as insulin neuritis, is seen in individuals with severe hypoglycemia that make abrupt, large improvements to glycemic control. Symptoms of neuropathic pain and autonomic dysfunction are prominent and develop within weeks after a change in glycemic control. Originally thought to be a rare disorder, this was seen in up to 10% of patients with diabetic neuropathy at a tertiary care referral center [46]. Although treatment-induced neuropathy is more commonly seen in younger individuals with type 1 diabetes, it can occur in older individuals who are unaware of their diagnosis of diabetes and enthusiastically initiate glycemic control. The risks of developing treatment-induced neuropathy occur with a decrease in the glycosylated HbA1c of more than 2 percentage points over 3 months in individuals with prolonged hyperglycemia (HbA1c elevated for 6 months or more) [46, 47].

11.4 Diagnosis and evaluation

The evaluation of a patient with a potential neuromuscular complication of diabetes begins with a thorough history and examination. Information regarding the type and duration of diabetes and the level of glycemic control must be ascertained. Poor glycemic control and long duration of diabetes are both associated with a significantly higher risk of neurological complications. A history of other diabetic complications, such as retinopathy, nephropathy or cardiovascular disease, should also be sought. The exact nature of onset as well as the constellation of clinical symptoms will help narrow the differential diagnosis. In general, a distal symmetric diabetic polyneuropathy will present with an insidious onset of sensory symptoms. Acute or subacute onset of symptoms should lead the clinician to consider one of the other diabetic-associated neuropathies. Sensory symptoms can be divided into positive and negative symptoms based on their characteristics. Positive symptoms include the presence of paresthesia, tingling, burning, and pain. Negative symptoms refer to lack of sensation such as numbness or loss of vibration and proprioception. Diabetic length-dependent neuropathies frequently involve a mixture of both small and large fibers, and clues to this are in the history. Symptoms of large fiber pathology include sensory ataxia and reduced touch sensation while symptoms of small fiber neuropathy would include pain, paresthesia, and diminished thermal sensitivity. The small fibers tend to be affected earlier than the large fibers [48]. Motor symptoms are a later manifestation, slow to progress, and also follow a length-dependent pattern [4]. In fact, if motor symptoms predominate an alternative diagnosis to DSPN should be considered. Focal weakness in the distribution of peripheral (including cranial) nerves will help identify entrapment or other focal mononeuropathies.

The history will help to guide the differential diagnosis in the evaluation of neuropathy in diabetes. An acute presentation of pain and autonomic symptoms could be treatment-induced neuropathy in diabetes. If there are motor manifestations (particularly if unilateral) the clinician should consider the possibility of diabetic radiculoplexus neuropathy. Symptoms of autonomic nervous system dysfunction can be broad and should be considered in the evaluation of patients with diabetes. Every organ system can be affected in an autonomic neuropathy: questions regarding cardiovascular, gastrointestinal, genitourinary, and sudomotor function need to be asked. Examples would include exercise intolerance, fatigue, palpitations, syncope, abdominal bloating, alternating diarrhea and constipation, anhidrosis, and dry skin (Table 11.1). The history should also investigate other potential causes of a neuropathy such as previous exposure to alcohol or neurotoxic drugs, nutritional deficiencies, kidney disease, neoplastic disease or paraproteinemias. Older individuals should be queried about changes in sensation as they may not report ongoing sensory symptoms if they are not experiencing pain.

The physical examination should be tailored to the individual based on their history. Orthostatic vital signs should include measurement of both supine and standing blood pressure and heart rate because of the risk of asymptomatic orthostatic hypotension. Older individuals can have transient, but significant, drops in blood pressure while standing that can increase their risk of falls [49].

The general examination should include inspection of skin for trophic changes and lack of hair as well as

Table 11.1 Symptoms associated with diabetic autonomic neuropathy.

System	Possible symptom
Cardiovascular	Resting tachycardia Exercise intolerance Orthostatic hypotension Silent myocardial ischemia
Sudomotor	Skin dryness Anhidrosis Heat intolerance Gustatory sweating
Genitourinary	Neurogenic bladder Erectile dysfunction Retrograde ejaculation Female sexual dysfunction
Gastrointestinal	Esophageal dysmotility Constipation Diarrhea Fecal incontinence Gastroparesis diabeticorum
Pupillary	Pupillomotor function impairment Argyll–Robertson pupil
Metabolic	Hypoglycemia unawareness Hypoglycemia-associated autonomic failure

inspection of feet for morphological changes. The neurological examination should in particular focus on sensation, strength, reflexes, and a gait examination when a distal symmetric diabetic polyneuropathy is likely, and focus on a cranial nerve examination when focal mononeuropathies are the underlying etiology. Particular attention should be given to the sensory examination. A 10 g monofilament should be used in a consistent fashion to document the presence of diminished protective sensation. The gait assessment should focus on the presence or absence of a sensory ataxia and for a positive Romberg sign. Decreased or loss of ankle reflexes and diminished vibratory sensation at the feet are clinical signs consistent with a distal symmetric sensorimotor polyneuropathy.

Neurological signs and symptoms can be complemented by the addition of certain electrophysiological tests. NCSs only evaluate large fiber function; in very early stages of neuropathy there may be predominant involvement of small unmyelinated nerve fibers, thus nerve conduction studies may be normal [50]. A normal NCS therefore does not rule out the presence of a small fiber neuropathy. NCSs provide invaluable information regarding the presence of a neuropathy, pattern of nerve involvement, and features that may suggest a primarily axonal or demyelinating pathophysiology or a combination of both. A typical diabetic polyneuropathy is characterized by a length-dependent pattern of abnormalities where the longer nerves are more vulnerable to injury and become affected first. In diabetes, sensory nerve fibers are generally involved earlier and to a greater degree than motor nerve fibers. A reduction in the sural sensory nerve action potential amplitude is often the initial finding, with a milder reduction in the common peroneal motor nerve action potential amplitude. A typical diabetic polyneuropathy is characterized by axon loss as the primary electrophysiologic feature. However, there are several reports in the literature of mixed axonal and demyelinating features being present in diabetic polyneuropathies [35]. The most common demyelinating feature seen in this context is slowing of conduction velocity. In type 1 diabetes this slowing of conduction velocity has been found to be associated with poor glycemic control and an improvement in control has led to a matched improvement in this particular parameter. The lack of features such as conduction block may reflect the diffuse nature of the nerve injury [34, 51, 52].

Aside from confirming the presence of a neuropathy, NCSs can serve as a useful baseline to track change over time. The NCS may identify the presence of demyelinating features which are more amenable to treatment and clinical improvement than axonal features. NCSs can also rule out other potential diabetic neuropathies, such as a radiculoplexus neuropathy. Focal mononeuropathies such as carpal tunnel syndrome, ulnar neuropathy, tarsal tunnel syndrome, and lateral femoral cutaneous nerve syndrome can all be identified through the various patterns identified with NCSs.

NCSs are generally well tolerated (although many patients do complain about the test), reproducible, and minimally invasive (if electromyography is performed). They are an objective measure of nerve fiber function that can define the presence and severity of a neuropathy. A disadvantage is that they only assess large fiber function and so may be completely normal in early diabetic neuropathies that only involve the small fibers.

Other neurophysiological techniques employed to diagnose neuropathy include quantitative sensory

testing (QST) and the quantitative sudomotor axon reflex test (QSART) [53]. QST assesses both small and large fiber function whereas the QSART assesses sudomotor (autonomic sweating) function [54, 55]. QST has the disadvantage that it is a psychophysical test and requires the patient to give their full attention and cooperation for the duration of the test. Although the sensory stimulus is an objective physical event, the response output represents the subjective report from a patient. QST can measure nerve fiber function through vibratory, thermal and painful stimuli, although a variety of other stimuli have been tried in the past. The American Academy of Neurology states that QST measuring vibratory and thermal thresholds is probably an effective tool in the documentation of sensory abnormalities in patients with a diabetic neuropathy [56]. The QSART is a non-invasive, reliable, and reproducible measure of sudomotor function. It measures an indirect sweating response through iontophoresis of acetylcholine of sweat glands [55]. For optimum reliability, the QSART requires meticulous attention to detail, including a constant environmental temperature. The QSART is a reliable measure of small fiber function and also gives specific information about the distribution of the neuropathy. In a length-dependent neuropathy there will be a distal to proximal gradient in the sweating response [57, 58].

A careful history and examination can direct which ancillary studies are indicated. These can be supplemented by specific diagnostic tests. A gastric emptying study can be performed for diagnosis of gastroparesis. Bladder function is assessed through urodynamic testing. Erectile dysfunction is a clinical diagnosis. However, any symptoms suggestive of erectile dysfunction warrant a full cardiovascular assessment because of the high associated risks of cardiovascular disease in individuals with diabetes.

Tests of sensory, motor, and autonomic nerve fiber function will confirm or refute the clinical diagnosis of a neuropathy. It should be noted that in some patients, especially those with neuropathies other than the DSPN, further tests may be warranted. Whilst NCSs may be normal early on in a DSPN and therefore potentially unhelpful, they are helpful in excluding other possibilities. Other neuropathies in diabetes, such as CIDP, radiculoplexus neuropathy, and focal mononeuropathies, can all be further evaluated. The cranial focal mononeuropathies are more likely to be ischemic in nature and in those instances an MRI brain with diffusion weighted imaging is warranted. Imaging of the spine may be helpful if the clinical picture suggests a radiculopathy. The decision to evaluate spinal fluid for elevated protein in the context of CIDP can also be decided based on the particular clinical scenario – it should be noted that protein may be elevated in patients with diabetic neuropathy [59]. Routine screening for a patient with diabetic neuropathy should include testing vitamin B_{12} levels, thyroid function, serum, and urine protein electrophoresis.

11.5 Management

The management of any patient with diabetes and neuromuscular complications takes a two-pronged approach. The first part is management of diabetes with an aim of improved glycemic control (while avoiding hypoglycemia) and the anticipated outcome of prevention of further complications with the possibility of improvement of the existing problems. The second part is symptom management achieved through both pharmacologic and non-pharmacologic measures. *In the elderly population a third prong is necessary and this includes a full assessment of the social situation, with a focus on level of independence and level of support available based on individual patient needs.*

The focus on glycemic control in the elderly will be discussed in detail in other chapters. Following optimization of a treatment plan for diabetes the next step in management involves symptom control. This involves measures to reduce pain associated with neuropathy, if present, but also to reduce adverse outcomes associated with the neuropathy. There are many options for treatment of a painful peripheral neuropathy. Pain associated with diabetic lumbosacral radiculoplexus neuropathy or many focal neuropathies will also be amenable to these treatments.

Neuropathic pain is may be difficult to treat effectively. The drugs used to treat neuropathic pain are very different to those used to treat pain that arises from inflammation or damage to tissues. Anti-depressant and anti-convulsant medications are the two most commonly used drug classes. Other drugs used include topical treatments, medicinal foods, and opioids. Review of all treatment options for neuropathic pain is outside the scope of this chapter. Several guidelines on the treatment of neuropathic pain in the setting of neuropathy have

Table 11.2 A summary of some of the medications used to treat pain in people with diabetic neuropathy.

Medication class	Medication	Dosage	Mechanism of action	Side effects
Antidepressants				
Tricyclics[1]	Amitriptyline	10–150 mg QHS	Inhibition of norepinephrine and serotonin re-uptake	Dry eyes, mouth, constipation, urinary retention, confusion
	Nortriptyline	10–150 mg QHS		
	Desipramine	10–150 mg QHS		
SNRIs	Duloxetine	60–120 mg QD	Inhibition of serotonin and norepinephrine uptake	Dizziness, somnolence, anorexia
	Venlafaxine	75–225 mg QD		Dizziness, somnolence, anorexia, EKG abnormalities
Anticonvulsants	Gabapentin	300–1200 mg TID	Inhibition of alpha-2-delta subunit of calcium channels	Fatigue, dizziness, leg edema, confusion, ataxia
	Pregabalin	50–200 mg TID	Inhibition of alpha-2-delta subunit of calcium channels	Fatigue, dizziness, leg edema, sedation
	Carbamazepine	Up to 200 mg QD	Inhibition of sodium channels	Dizziness, somnolence, nausea, leucopenia
Opioids	Tramadol	50–100 mg BID	μ-opioid receptor agonist, modulates nociception	Nausea, constipation, headache
	Tapentadol	50–100 mg Q4-6H Max. 600 mg/24 h	Opioid spinal-supra-spinal synergy	Nausea, constipation, headache
	Oxycodone	10–30 mg BID		Somnolence, nausea, constipation
Antioxidant	Alpha-lipoic acid	200–1800 mg QD (PO or IV)	Antioxidant, anti-inflammatory	Gastrointestinal discomfort
Topical product	Capsaicin cream	Topical cream	Activation of the TRPV1 channel and eventual depletion of substance P	Burning pain on application

[1] Based on the Beers criteria, tricyclic antidepressants should not be used in individuals over the age of 65 and therefore are not appropriate for use in the elderly population [65].
SNRI, serotonin and norepinephrine reuptake inhibitor; QHS, every bedtime; QD, four times daily; TID, three times daily; BID, twice daily; Q4-6H, every 4–6 h; TRPV1, transient receptor potential cation channel subfamily V member 1 (TrpV1).

been published [60–62]. When treating neuropathic pain the potential adverse effects need to be weighed against the potential benefits. This is especially important in an elderly population, where risks of adverse events are higher. Table 11.2 reviews some of the most common treatments and the associated concerns in the elderly.

The symptoms of a painful diabetic neuropathy are often worse at night and potentially interfere with sleep. Patients who are sleep deprived have higher pain levels [63, 64]. This should be taken into account when deciding a treatment regime. Although many of the treatments for neuropathic pain (such as the tricyclic antidepressants) have sedating properties as one of their side effects and are often used to aid with sleep, the Beers criteria identify an increased risk to the elderly with these medications [65].

The American Academy of Neurology recommends pregabalin (level A evidence) as a first-line treatment for neuropathic pain [61]. Gabapentin, amitriptyline, venlafaxine, and duloxetine can also be used (level B evidence) [61]. Venlafaxine may be added to gabapentin for a better response (level C evidence). Capsaicin cream can be considered (level B evidence) and a Lidoderm patch (level C evidence) [61].

11.5.1 Foot care

Appropriate foot care in the elderly patient with diabetes is an integral part of a neuropathy evaluation. In individuals with sensory neuropathy, diminished cutaneous sensitivity increases the risk of painless injury and a simple cut may become infected, leading risks of amputation. When protective sensation is lost, the inability to sense foot pressure can predispose to foot ulceration. Charcot joints are a late complication of progressive diabetic neuropathy. The podiatric complications are more likely in an older patient population and daily foot inspection should be strongly encouraged. The elderly are also the patients who are at a greater risk of falls. Early referrals to podiatry can prevent minor injuries from becoming major complications.

11.6 Summary

In summary, diabetic neuropathy is a prevalent condition that has various clinical presentations, but the traditional length-dependent neuropathy is the most common [8, 9]. Neuropathy is associated with significant morbidity and mortality, especially in an elderly population [3]. Regular screening can help identify subclinical neuropathy and will reduce the development of complications. Ancillary investigations may be necessary to make a specific diagnosis or to define the severity of the problem [11]. Risk factors for neuropathy progression include hyperglycemia, hyperlipidemia, smoking, alcohol use, and inactivity [66]. Risk reduction should therefore target glycemic control, lipid control, smoking cessation, alcohol reduction, and physical activity. For symptomatic treatment of painful neuropathy there are many options available [67]. Adverse drug reactions are likely to be more frequent in this population, compounded by the risk of polypharmacy, so should be considered in the management plan. Assessment of the home situation, fall risks, and foot care are of paramount importance in the overall clinical care of the patient. Education of patients and family members regarding patient safety in the home can also help prevent or reduce morbidity.

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CHAPTER 12
Sensory disabilities in people with diabetes

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KEY MESSAGES

- Impairment of vision, hearing, smell, taste, and bodily sensation are common in people with diabetes, adding to the effects of aging.
- Many diabetic complications, for example retinopathy, can be prevented.
- Seek sensory disability; if present, find and manage treatable causes or symptoms. Identify and treat depression.
- Ensure appropriate communication. Provide support and safety advice.
- Get expert help where needed.

12.1 Introduction

It has been suggested that Shakespeare himself played the part of Adam in "As You Like It". Adam, aged four score years, said "Though I look old, yet I am strong and lusty" (Act II, Scene iii). Adam had not yet reached the seventh age of man: 'Sans teeth, sans eyes, sans taste, sans everything' (Act II, Scene vii).

12.2 The five senses

Traditionally, the five senses are vision, hearing, smell, taste, and bodily sensation (touch, temperature, position, vibration). All these senses can be reduced in older people. All these senses are more likely to be impaired in people with diabetes, mostly because of complications of diabetes. So elderly diabetic patients face significant sensory disability. Older people are highly likely to suffer combined sensory disabilities, leading to reduced quality of life and risk of harm. Young people with diabetes may also experience significant sensory disability.

12.3 Prevent sensory disability

There is clear evidence for the potential preventability of diabetic complications such as retinopathy and neuropathy. The other sensory abnormalities associated with diabetes have been less studied but smoking impairs smell and taste, and neuropathy, retinopathy, and cardiovascular disease appear more common in diabetic patients with some sensory disabilities.

It is likely that good control of blood glucose, blood pressure, and cholesterol combined with healthy eating, limited alcohol intake, weight control, regular exercise, and not smoking will reduce the likelihood of sensory disability among older people with diabetes and may slow progression of impairment. We should all avoid excessive noise and risk factor management should be tailored safely to each individual person's situation [1].

Diabetes in Old Age, Fourth Edition. Edited by Alan J. Sinclair, Trisha Dunning, Leocadio Rodríguez Mañas, and Medha Munshi.

Table 12.1 Estimated numbers of people living with disorders that can impair vision (RNIB sight loss data tool).

Eye condition	2015	2016
Late-stage age-related macular degeneration	588,659	660,486
Late-stage wet age-related macular degeneration	417,295	468,741
Late-stage dry age-related macular degeneration	203,019	226,952
Cataract	642,711	731,682
Glaucoma	588,417	618,403
Background diabetic retinopathy	1,126,342	1,185,778
Non-proliferative and proliferative diabetic retinopathy	128,725	135,517

Data from RNIB sight loss data tool, http://www.rnib.org.uk/knowledge-and-research-hub/key-information-and-statistics.

12.4 Seeing

12.4.1 Visual impairment in the general population

Blindness is perhaps the most feared sensory loss. Visual impairment is estimated to affect 285 million people worldwide, of whom 39 million are blind (82% aged ≥50 years) and 246 million have low vision. The World Health Organization (WHO) states that "Globally the major causes of visual impairment are:

- uncorrected refractive errors (myopia, hyperopia or astigmatism), 43%
- unoperated cataract, 33%
- glaucoma, 2%."

WHO also states that "80% of all visual impairment can be prevented or cured" [2].

The number of people living with sight loss in the UK increases with age: 65–74 years 354,346, 75–84 years 508,757, ≥85 years 871,909 (Table 12.1) [3].

12.4.2 Visual impairment in people with diabetes

A 2010 US estimate showed 7,685,237 people with diabetic retinopathy (0.05% of the total US population). 45% of retinopaths were ≥64 years of age [4].

Boxes 12.1 and 12.2 list visual problems resulting from diabetes mellitus and accompanying advice to minimize their impact. What effect do these have on what the patient sees? The most common visual problem is visual blurring due to high glucose concentrations, which may change with changing blood glucose levels.

Diabetic retinopathy impairs color vision. The Early Treatment Retinopathy Study [5] found that about 50% of patients had abnormal hue discrimination. Factors most strongly linked with reduced color discrimination were age, the severity of macular edema, and the presence of new vessels. Laser treatment may also alter color vision. It is necessary to avoid visually-read blood glucose testing strips that rely on matching color change. People with diabetes may also have impaired vision in dim light or at night.

Macular edema can blur central vision and impair focusing. Laser treatment often reduces the visual field and affects night and color vision [6].

Stroke may cause homonymous hemianopia, which usually precludes driving in the UK [7].

All these problems may make everyday life harder. Specific issues for diabetes care could be eating and checking food content or cooking instructions, reading medication names or instructions, entering insulin dose on a syringe, insulin pen or pump, reading finger-prick blood glucose test results, reading clinic appointment letters or medical information, telephoning for help, and reading direction signs in health facilities. Many visual aids are available, for example from the Royal National Institute of Blind People (RNIB) in the UK.

12.4.3 Charles Bonnet syndrome

Charles Bonnet syndrome – complex visual hallucinations in visual impairment – is found, if sought, in 11–60% of patients with poor visual acuity. It is most prevalent in those aged >64 years [8, 9]. Patients rarely volunteer these symptoms and are reassured to discover

Box 12.1 Visual problems among people with diabetes.

Blurred vision
Fluctuating vision
Impaired color vision
Impaired night vision
Impaired central vision
Reduced visual field
Reduced depth perception
Blind spots or gaps in vision
Curtains, veils, clouds, red streaks or black dots in vision

Box 12.2 Advice for patients with impaired bodily sensation.

Look after your feet.
Don't walk bare foot.
Buy properly fitting shoes.
Are you safe to drive?
When handling hot pans wear well-fitting oven gloves that cover the wrist.
Use a bath thermometer.
Do not sit close to a fire or radiator.
Do not use hot-water bottles.
Protect your feet and hands in cold weather.
Take care getting things out of the freezer.
Wear gloves when gardening.
Consider using aids, devices or equipment to help you do things or get about.
Ask your pharmacist for advice about handling and taking your medication.
Use your eyes to help keep your balance and to keep what you are carrying steady.

that their cause is the visual problem and not mental illness. Temporary visual impairment is common in hyperglycemia. A 72-year-old woman with hallucinations was diagnosed with type 2 diabetes. The hallucinations improved with glucose control [10].

12.4.4 Guide patients to eye checks and potential help

In the UK, sight tests are free for everyone aged ≥60 years. Also free are annual NHS England diabetic eye screening checks for people with diabetes aged >12 years [11]. Similar schemes are available in other nations. In 2011–12, 2,587,000 people with diabetes were identified in England, 73.9% of whom had eye screening. The uptake of the screening offered was 80.9%.

Patients should be asked if they have difficulty seeing. If new or unresolved problems emerge, patients should be referred for eye tests or specialist ophthalmology.

In the UK, the Certificate of Vision Impairment (CVI) formally certifies a person as either sight impaired (partially sighted) or severely sight impaired (blind) [12]. The CVI is passed to the local social services department, which is required to contact the patient. This can lead to state benefits such as an attendance allowance or personal independence allowance.

It is important that patients receive eye checks regularly and that those with visual impairment receive appropriate support and benefits.

12.4.4.1 Communicating with people who have visual impairment

Visual impairment should be recorded and information provided in large print, or by voice recording. In the UK the RNIB provides support and advice (http://www.rnib.org.uk/).

Presbyopia is part of normal aging among people over 40 years. There is a case for producing all patient communication and information in larger print as most patients are likely to be over 40, and other visual problems become more common with age.

12.5 Hearing

12.5.1 Hearing impairment in the general population

A 2007 report stated that "About one in five adults in the UK has a bilateral hearing problem that affects their hearing and communication. The major problems occur in listening to speech in a background of noise … which makes communication or enjoyment very difficult. Previous estimates have suggested that at least one in ten people might benefit from amplification, but currently only one in six of those who might benefit have and fully use their amplification (hearing aids and assistive listening devices), and a further one in six are not receiving substantial benefit from their aids.

Typically, those who are referred for hearing assessment recognize that they have had a hearing problem for around 10 years or more, are aged in their mid-70s and have a substantial hearing problem. The older that people are when they present for assessment

and intervention, the more difficult they find adaptation to and care of their hearing aids." [13].

Among people aged 55–74 years 12% had a hearing problem causing moderate or severe worry, annoyance or upset, 14% had a bilateral hearing impairment of at least 35 dB hearing level, but only 3% had a hearing aid. One in four were then shown to be helped by providing hearing aids. In this study, the authors concluded that screening would be appropriate [14].

In 2011, Action for Hearing estimated that >10 million people in the UK had hearing loss, of whom 6.4 million were aged >65 years [15]. Most 80-year-olds have some hearing impairment. Up-to-date prevalence studies are needed.

US estimates for disabling hearing loss (1999–2010 data) were 2% of 45–54-year-olds, 8.5% of 55–64-year-olds, nearly 25% of 65–74 year-olds, and 50% of those aged ≥75 years [16].

12.5.2 Hearing impairment in people with diabetes

Deafness is more common among people with diabetes than in those without. A meta-analysis of 13 studies found that the pooled odds ratio (OR) (95% confidence interval, CI) of hearing impairment for people with diabetes compared with non-diabetics was 2.15 (1.72–2.68). The OR was 2.61 in people with mean age ≤60 years and 1.58 in those aged >60 years. Matching patients by age or gender did not affect the results, nor did excluding those who had worked in a noisy place [17].

A UK observational study in primary care found that referral rates of patients with diabetes were nearly double those of the non-diabetic population (7.5% vs 4%). Most patients with hearing loss (84.1%) had high-frequency sensori-neural hearing loss. Loss of protective sensation on the 10-g monofilament test (OR 3.2, CI 1.6–6.5) and vibration sense (OR 2.6, CI 1.2–5.6) was significantly higher in those with hearing loss than in a group with type 2 diabetes and normal hearing. The hearing-impaired group had almost twice the rate of at-risk feet (37.7% vs 20.1%) (OR 2.4, CI 1.4–4.2). Pre-existing cardiovascular disease was the only pre-morbid condition that was associated with hearing loss (OR 1.8, CI 1.1–3.2). There were no differences in HbA1c and lipids [18].

An Australian group followed a population for 10 years. They were aged ≥49 years at baseline. Among those with type 2 diabetes, after adjusting for risk factors, 50.0% had age-related deafness compared with 38.2% of non-diabetics (OR 1.55, CI 1.11–2.17). Progression of hearing loss was greater in those with newly diagnosed diabetes than in people without diabetes [19].

The UK National Screening Committee does not yet consider there is sufficient evidence for general population screening for hearing loss. More evidence is also required for audiological screening in people with diabetes but deafness is common in older people with diabetes and the relevant studies should be done. At the annual diabetic review, and at any time the patient does not appear clearly to understand communication, practitioners should ask "Can you hear me alright?" and record the answer in the record. Patients with hearing impairment should be referred for formal audiological testing.

12.5.3 Causes of hearing loss in people with diabetes

The pathogenesis of hearing loss is difficult to study in life but it seems likely that both neuropathy and microvasculopathy contribute in diabetes. Several syndromes involve both diabetes and deafness, including Alström's, Hermann's, Roger's, and Wolfram's. Sadly, many of these patients do not live to be elderly. The same applies to congenital rubella syndrome.

Maternally-inherited diabetes and deafness (MIDD) can present at any age, including those aged >60 years. It may affect up to 1% of the UK diabetic population, misdiagnosed as type 1 or type 2 diabetes. It is important to recognize this mitochondrial disorder. In addition to a high risk of deafness, it may present at a young age, and patients may also have cardiac, renal, muscle, retinal, gut and other health problems. Diagnosing MIDD at any age allows screening of female relatives (both men and women can have MIDD, but only women can pass it on). Metformin may affect mitochondrial function so another glucose-lowering treatment should be used. MIDD should be sought in patients with diabetes and deafness, and a history of diabetes in female relatives.

12.5.4 Communicating with people who have hearing impairment

Most diabetes care requires full communication between the patient and healthcare professionals. Patient education is essential for optimal care. Any degree of hearing loss can significantly impair communication.

Missed telephone calls or unanswered door bells distress both the patient and his or her concerned relatives. Deafness can also be dangerous, for example not hearing approaching traffic when crossing the road, missing urgent verbal warnings or failing to hear safety information given during consultations.

Patients with profound hearing loss from a young age often use sign language. Like other languages this varies internationally, and there will be regional dialects. Such patients may have problems reading written words if signing was their first language. A properly trained signer and at least double the usual appointment time should be arranged to ensure full communication. The chapter author once met a patient with no hearing who had had diabetes for over 20 years yet no-one had ever taken the time to explain what diabetes actually is.

Combined visual and auditory impairment is common and may mean that patients find it difficult to hear or read information. Patients with severe visual and hearing loss, "deaf-blind" people, can learn touch sign language. An appropriate interpreter should be arranged for clinic visits. The difficulties of handling tiny hearing aids when you cannot see them properly is so well known that some hearing aid services routinely supply spare devices to patients with visual impairment. This problem is worsened by peripheral sensory neuropathy.

National schemes provide help. Texting and email are useful, as are textphones. Diabetes UK has video information about diabetes for people who use British Sign Language [20]. Action on Hearing Loss provides advice and support for people with hearing impairment and their carers, including advice on equipment (http://www.actiononhearingloss.org.uk/).

12.6 Smelling and tasting (olfaction and gustation)

As with hearing, both smell (olfaction) and taste (gustation) can be impaired in diabetes yet the pathophysiology is still unclear. The consequences can seriously impair quality of life and safety. Much of the enjoyment of eating comes with the smell and taste of food. A good sense of smell is important to appreciate the full flavor of food. Failure to smell smoke or gas could be fatal.

Clinicians rarely ask patients about olfaction or gustation, and patients rarely volunteer these symptoms unless marked. Many may not realize how impaired their senses of smell or taste are.

12.6.1 Smell and taste in the general population

Smell and taste are difficult and time-consuming to test. Assessments should be corrected for age, gender, smoking, alcohol, and cognitive problems among other variants. While anosmia or ageusia are obvious, more subtle abnormalities may be missed.

A US study formally tested smell and taste in 3005 people aged 57–85 years. Taste was more likely to be impaired than olfaction, with 14.8% suffering severe gustatory dysfunction and 2.7% severe olfactory dysfunction. Performance on both the smell and taste tests was independently associated with age, educational level, and sex. Food smells were better identified than non-food smells. Older people, those with a lower educational level, and male sex were all associated with lower scores. Patients with symptoms of depression had lower odor identification scores [21].

12.6.2 Smell in the general population

A US study found a prevalence of impaired olfaction of mean (SD) 24.5% (1.7%). The prevalence increased with age: 62.5% (57.4–67.7%) of 80–97-year-olds had olfactory impairment. Impairment was more common among men (adjusted prevalence ratio 1.92, 1.65–2.19), and current smoking, stroke, epilepsy, nasal congestion or upper respiratory tract infection also increased prevalence of olfactory impairment. In this study self-reported olfactory impairment was low (9.5%) and this latter measure became less accurate with age. In the oldest group, aged 80–97 years, sensitivity of self-report was 12% for women and 18% for men [22].

The most common causes of impaired smell (hyposmia) are nasal and sinus disease, upper respiratory tract infections, head injury, and neurodegenerative disorders. The most common causes of impaired taste (hypogeusia) are oral disorders such as periodontal disease, dentures and other oral appliances, dental procedures, and Bell's palsy [23].

12.6.3 Smell in people with diabetes

A Swedish study found olfactory dysfunction in 19.1% of 1387 adults tested, including 13.3% with hyposmia and 5.8% with anosmia. Impaired olfaction was associated with aging, male sex, and nasal polyps, but not

diabetes or smoking. However, among those with anosmia, diabetes mellitus and nasal polyps were risk factors [24].

French patients with type 1 diabetes of over 1 year's duration had significantly poorer sense of smell than controls, a finding confirmed by univariate and multivariate analyses, including age, sex, body mass index, blood pressure, smoking, and alcohol. Among patients with diabetes increasing age, diabetes duration, microalbuminuria, and peripheral neuropathy all reduced olfaction [25].

Among 154 adults (119 with type 2 diabetes), multivariate analysis found that type 2 diabetes and hypertension were independently associated with poorer olfactory scores. Scores for both odor threshold and odor identification were reduced among people with diabetes. Scores were lower in the presence of diabetic peripheral neuropathy or retinopathy. People with uncomplicated diabetes had the best olfactory score. Olfactory score was not correlated with glycated hemoglobin [26].

Altered smell and taste sensation may be an early sign of dementia or Parkinson's disease, although the link with the latter has been questioned. Subjects affected by mild cognitive impairment (MCI) were studied longitudinally. After 2 years of follow-up, the 47% of MCI olfactory-impaired subjects and the 11% of MCI olfactory-normal subjects progressed to dementia. A lower mental test score and significant impairment of olfaction at baseline were independently associated with the progression to dementia within 2 years [27].

The US National Social Life, Health and Aging Project assessed olfaction with Sniffin' Sticks in 3005 community dwelling adults aged 57–85 years in 2005–2006. In 2010–11 they noted who had died. The authors stated: "Mortality for anosmic older adults was four times that of normosmic individuals while hyposmic individuals had intermediate mortality ($p<0.001$), a 'dose-dependent' effect present across the age range. In a comprehensive model that included potential confounding factors, anosmic older adults had over three times the odds of death compared to normosmic individuals (OR, 3.37, CI 2.04–5.57)), higher than and independent of known leading causes of death, and did not result from the following mechanisms: nutrition, cognitive function, mental health, smoking and alcohol abuse or frailty." People with diabetes were identified and the same effect was noted in this group [28]. These findings have yet to be repeated.

12.6.4 Taste in people with diabetes

A French study which compared electro- and chemical gustometry found that 73% of patients with type 1 diabetes had impaired taste compared with 16% of the non-diabetic controls. For the whole population multivariate analysis found that taste sensation worsened with greater age, smoking, and higher glucose level. Among the diabetic group, 78% of those with complications had impaired taste versus 44% of those without complications. In this group, hypogeusia was linked with age and diabetes duration, and with peripheral neuropathy, but not with glycemia. Taste impairment particularly applied to sucrose or similar tastes [29].

Duration of diabetes may be relevant. Electrogustometry found that people with newly diagnosed type 2 diabetes had impaired ability to taste glucose, which improved with improving glucose control. A group of neuropathic patients with established diabetes had impaired electrical and chemical thresholds for taste but less so than the newly diagnosed patients [30].

Dry mouth due to hyperglycemia is common. People with diabetes may have glossitis or atrophic patches on their tongues. They are more prone to gingivitis, periodontal disease, burning mouth syndrome, and other oral diseases such as candidiasis.

12.6.5 Smell and taste and neuropathy

Smell and taste rely on the normal function of cranial nerves I, V, VII, IX, and X. Cranial diabetic neuropathies account for 0.05% of all diabetic neuropathies and usually involve III, IV, VI, and VII. They are thought to be due to microvascular infarcts [31].

Cranial neuropathies may be more common than is supposed. Cruccu *et al.* found that 13/23 patients with severe diabetic polyneuropathy had mandibular trigeminal dysfunction on testing [32].

Impaired olfaction in people with diabetes versus controls was found in a Canadian study. Among people with diabetes it was those with painful diabetic neuropathy who had significantly impaired olfaction. The authors postulated that neuropathic pain may impair performance on olfactory testing in people with diabetes [33].

Diabetic autonomic neuropathy can cause gustatory sweating, facial sweating precipitated by spicy or highly flavored foods. Avoiding these foods may help and anti-muscarinic drugs, for example propantheline, are

sometimes used. Other evidence of autonomic neuropathy, for example postural hypotension, should also be sought.

12.6.6 Treatment of smell or taste impairment

The first step is for patient and clinician to recognize that there is a problem. Complete lack of smell or taste will make patients seek help, but more subtle abnormalities may not be noticed. Clinicians rarely test olfaction or taste, and rarely have the relevant equipment (or know precisely how to use it). Treatable causes such as nasal or sinus disease (e.g., polyps), or oral problems should be sought first. Medication should be reviewed (see Box 12.3). Ear, nose and throat, or dental referral is required for detailed assessment.

Patients with olfactory impairment should be advised to install smoke detectors and gas detectors in their houses. Those with gustatory impairment should be warned of the need for care with unfamiliar or very spicy foods. Patients who have problems tasting sugar should be advised to avoid it, not increase it.

In many cases little treatment can be offered. Regular dental review and good oral and dental hygiene should be advised. Smokers should be advised to stop and helped to do so. Artificial saliva may alleviate a dry mouth. Poor glucose control could be improved, although there is no evidence that this will improve the sense of smell or taste. Other risk factors should also be improved. If specialists suspect inflammatory or autoimmune processes they may use steroids to manage glucose imbalance.

12.7 Impaired bodily sensation

12.7.1 Impaired bodily sensation in the general population

Impairment of bodily sensation, for example touch or temperature, may not be noticed or reported unless it is severe. Peripheral neurological testing was performed on 795 patients aged ≥65 years registered with family physicians in Oklahoma. Neuropathic symptoms were sought, and tests included ankle reflexes, position sense,

Box 12.3 Drugs that may cause sensory impairment.

May impair vision: ACE inhibitors (e.g., captopril, enalapril, ramipril), antibiotics (e.g., ciprofloxacin, ethambutol, isoniazid, linezolid, metronidazole, nitrofurantoin, tetracycline, trimethoprim), anticholinergic agents (e.g., atropine), anti-inflammatories (e.g., naproxen, diclofenac), cancer treatments (e.g., busulfan, carboplatin, cisplatin, paclitaxel, tamoxifen, vincristine), baclofen, cardiovascular drugs (e.g., amiodarone, atorvastatin, furosemide), chloroquine, chlorphenamine, didanosine, glucose-lowering drugs (e.g., glipizide), glucocorticoids (e.g., prednisolone, dexamethasone), phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil), pregabalin, psychiatric drugs (e.g., chlorpromazine, haloperidol), retinoids (e.g., retinoic acid), sulfa-based drugs (e.g., sulfasalazine).

May impair hearing: antibiotics (e.g., ciprofloxacin, gentamicin, neomycin, streptomycin, vancomycin, tobramycin), anti-inflammatories (e.g., aspirin, diclofenac, ibuprofen, naproxen), atorvastatin, cancer treatments (e.g., cisplatin, carboplatin, vincristine), chloroquine, quinine, sulfasalazine, tadalafil.

May impair smell or taste: antibiotics (e.g., ciprofloxacin, metronidazole), antidepressants (e.g., fluoxetine), anti-epileptic drugs (e.g., phenytoin), anti-thyroid drugs (e.g., carbimazole, propylthiouracil), baclofen, cancer treatments (e.g., cisplatin, docetaxel), cardiovascular drugs e.g. ACE inhibitors e.g. captopril, ramipril; antipsychotics (e.g., lithium), glucose-lowering drugs (e.g., metformin, glibenclamide), gout treatments (e.g., allopurinol, colchicine), levodopa/carbidopa, pregabalin, steroids (e.g., prednisolone), long-term use of nasal decongestants may impair sense of smell.

May impair peripheral nerve sensation: antibiotics (e.g., ciprofloxacin, ethambutol, isoniazid, linezolid, metronidazole, nitrofurantoin), anti-epileptic drugs (e.g., carbamazepine, phenytoin), anti-retroviral drugs (e.g., didanosine, stavudine), arthritis treatments (e.g., sodium aurothiomaleate (gold), etanercept, infliximab, leflunomide), cancer treatments (e.g., cisplatin, docetaxel, doxorubicin, docetaxel, paclitaxel, vincristine), cardiovascular drugs (e.g., amiodarone, atorvastatin, hydralazine, rosuvastatin), chloroquine, dapsone, endocrine/metabolic drugs (e.g., carbimazole, etidronate), phenytoin, gout treatments (e.g., allopurinol, colchicine), psychiatric drugs (e.g., amitriptylline, lithium).

This list is not exhaustive. If your patient has sensory impairment check if their past and present medication may be implicated using an official source, for example the summary of product characteristics or the British National Formulary (http://www.medicinescomplete.com/about/publications.htm).

vibratory sense, fine touch sensation, balance, and a 50-foot timed walk. At least one bilateral sensory deficit was found in 26% of those aged 65–74 years, 36% of 75–84-year-olds, and 54% of those aged 85 or more. Just 40% of those with a bilateral sensory deficit were known to have a condition causing neuropathy. Predictors of bilateral deficits included increasing age, income less than $15,000, a history of military service, increasing body mass index, self-reported history of diabetes mellitus, vitamin B_{12} deficiency or rheumatoid arthritis, and absence of a history of hypertension. Deficits were associated with numbness, pain, restless legs, trouble walking, trouble with balance, and reduced quality of life [38]. Among those with diabetes, 47% had a bilateral sensory deficit [34].

12.7.2 Diabetic neuropathy

Diabetic neuropathy is discussed in detail in Chapter 11. Sensory abnormalities are most likely to be due to peripheral sensory neuropathy, whether painful or not. Insulin neuritis or entrapment syndromes also cause sensory impairment.

Symptoms of diabetic peripheral neuropathy include reduced touch, numbness, prickling and/or tingling sensation, burning feelings, aching pain, tightness (like a sock or stocking), sharp, shooting or stabbing pain, dysesthesia, allodynia, and hyperalgesia. The skin may feel dry.

12.7.3 Sensory impairment in cerebrovascular disease

Cerebrovascular events are common among people with diabetes and often produce a sensory deficit. Touch sensation is impaired on the affected side in up to 85% of people immediately after a stroke. About 25% of patients notice sensory impairment on the side without motor involvement or abnormal peripheral sensation or interpretation of peripheral stimuli.

Patients at least 3 months after a unilateral stroke with hemiparesis affecting an upper limb were tested in the hand with monofilaments. A third showed impairment of cutaneous function [35].

A UK study of 70 patients on average 15 days post stroke found that "somatosensory impairment was common after stroke; 7–53% had impaired tactile sensations, 31–89% impaired stereognosis, and 34–64% impaired proprioception." Stroke severity was the main influence on initial impairment, and initial sensory impairment was the main influence on subsequent impairment [36]. Proprioception and stereognosis are more likely to be impaired than tactile sensation. The degree of sensory loss is linked with stroke severity and motor dysfunction [37].

12.7.4 Spinal cord problems and diabetes

Diabetes appears to be a risk factor for the rare condition of spinal cord infarction [38]. Spinal myelopathy has also been described in diabetes. An autopsy study in 1978 found this in 41% of 75 consecutive post-mortems on diabetic patients. Posterior column demyelination was described in 27% of all the patients, and spinal cord infarcts in 19% [39].

12.7.5 The consequences of impaired bodily sensation

"The sensation on the bottom of my feet, like I am walking on balloons, along with balance problems, add up to constant fall possibilities. Family and friends don't understand that this condition, in many ways, takes hold of your life and you are harder to live with." (quote from Thomas, aged 75 or over [40]).

The sensory abnormalities of cerebral or spinal damage vary and can seriously impair rehabilitation. The numbness, dysesthesia or pain of diabetic neuropathy can occur anywhere but are most common in the feet and lower legs in a stocking distribution. Numb feet can lead to pressure trauma, especially on the soles, and injury from sharp objects or damaged or badly fitting shoes. Shoes may be laced too tight. Drivers with absent foot sensation will not be able to feel the pedals (e.g., the brake) and should have a car with fully manual controls and automatic gears. Numb feet can cause tripping and stumbling. Lack of proprioception affects walking and balance, producing a wide-based gait and increasing the risk of falls. Patients may be accused of being drunk or "on something."

Neuropathy in the hands makes it hard to pick things up and hold them. Items are often dropped. Patients have to grip objects painfully hard to ensure they don't drop them and find eating in company or shopping embarrassing. Writing may be challenging, as may using a touch-pad phone or a keyboard. Impaired temperature sensation risks burns when cooking or from heating appliances, or cold injury, even frostbite, in icy weather or with frozen items.

Patients with diabetic neuropathy often have erectile dysfunction as well as other complications such as retinopathy.

12.7.6 Treatment of sensory impairment

Peripheral neuropathy is difficult to treat, as are other sensory losses, for example from stroke (although this may improve with time). A full assessment is essential, particularly to exclude treatable causes of neuropathy, as these often coexist, for example vitamin B_{12} deficiency in patients on metformin or in pernicious anemia. Medication and glucose control, as well as other risk factors, should be reviewed and improved.

Neuropathy, especially if painful, is often associated with depression, which should be sought and treated. A UK study of 494 patients with diabetic neuropathy, mean age 62 years, found that both neuropathy disability score and vibration perception threshold significantly influenced the Hospital Anxiety and Depression Score. This was particularly so with the patients' perception of the unpredictability of diabetic neuropathy symptoms and lack of control by treatment, and the restriction of activities of daily living [41]. In Chapter 11, the management of painful neuropathy is discussed.

Patients also want relief from non-painful neuropathic symptoms. Improving glucose control is important in slowing progression. Avoid over-rapid glucose fall and hypoglycemia, which is especially dangerous in these patients who are likely to have autonomic neuropathy. Exercise strengthens muscles and improves balance, and might help improve the neuropathy. An initial small study of 17 subjects with diabetic peripheral neuropathy showed that exercise improved symptoms and increased intra-epidermal nerve fiber branching. Further larger studies are needed [42].

There have been multiple attempts to develop medications to improve neuropathic symptoms, and studies continue. While some drugs may reduce the distress of painful neuropathy, none have so far reversed the underlying nerve damage sufficiently for them to be released generally for this purpose. As neuropathy progresses there is potential for reversal but once the patient has no sensation left, for example complete numbness, reversal is very unlikely to be feasible without new nerves. This is a very difficult area to study. Sensation testing requires precision. While some outcomes are measurable, for example nerve conduction, sensation is by definition dependent on the individual's personal perception, so is influenced, for example, by mood. Good placebo controls are essential.

All patients with impaired bodily sensation should be taught how to stay safe (see Box 12.2). People with profound diabetic peripheral neuropathy sitting by the fire have been alerted to their legs burning solely by the smell of scorched flesh. People with diabetes and their carers should learn how to use the Diabetes UK touch the toes test, and use it [43].

12.8 Medication and sensory impairment

Vision, hearing, smell, taste, and peripheral sensation can all be impaired (or occasionally completely destroyed) by medication. Take a full medication history (including past medication) in patients with sensory impairment. The route of excretion will influence potential medication toxicity, for example renally excreted drugs can accumulate in renal impairment. Box 12.3 lists some drugs that have been implicated in sensory loss.

12.9 Sensory assessment

Undergraduate and postgraduate teaching of neurological assessment is variable. Many medical students feel they are not good at neurological examination and do not enjoy doing it. This has been termed "neurophobia" and is also common among qualified doctors [44].

The assessment of sensory impairment – vision, hearing, smell, taste, pain, temperature, position, and vibration – is often regarded as time-consuming and complex so is frequently omitted from routine neurological assessment by non-neurologists. More detailed assessment is rarely performed. Sensory impairment is so common among older people that it must be properly assessed. Neurophobia must be recognized and treated!

12.10 Conclusions

As we age we are all at risk of losing some of our vision, hearing, sense of smell and taste, and bodily sensation. Having diabetes increases the risk of impairment of all

these sensory functions. Older people with diabetes are therefore highly likely to have impairment of one or more sensory modalities, which can seriously impair their ability to perform the activities of daily living and can ruin quality of life. Falls are common. Life can become a real struggle. Depression is common.

As healthcare professionals we often focus on the numbers: what is the HbA_{1c}, the blood pressure, creatinine, retinopathy grade? The patient is focused on how their diabetes and its complications affects his or her life: numbness may be much more important than numbers. What can your patient with diabetic retinopathy actually see: can he or she see you? Can he or she even see a big red bus [45]?

All the senses should be assessed in people with diabetes. If abnormalities are found, treatable causes should be sought and, if found, treated. All findings and their implications should be explained to the patient and the patient helped to improve his or her glucose balance and other diabetes self-care. People with diabetes who have significant sensory disability should, with their carers, be provided with safety information. They can be referred to the relevant specialist service, as well as for occupational health and physiotherapy assessment. They should be guided to social support and any benefits to which they may be entitled (or referred to an organization that can help them do this). Sensory problems should be recorded prominently in clinical records and staff caring for the patient, for example in hospital, must be made aware of these disabilities. Patients with difficulty seeing or hearing should be given the time they need using the best form of communication for each patient. Appropriate interpreters should be arranged if needed. Practitioners should ensure that patients have understood what they have said. Above all patients with sensory disability should be managed with patience, sensitivity, and kindness.

More research is needed on many aspects of sensory disability, including the practical effects of these disabilities on patients' everyday lives and how best to help.

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CHAPTER 13
Sexual health and wellbeing

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KEY MESSAGES

- It has become less acceptable to merely dismiss bothersome symptoms such as excessive tiredness, poor concentration, altered mood, depression, and sexual dysfunction as merely a consequence of the normal aging process.
- Androgens and estrogens are now known to play important roles in cardiometabolic disease but little attention has been paid to this within current medical and urological education.
- In diabetes there is good evidence that sexual problems are strongly associated with depression in both men and women.
- There is high-level evidence that testosterone replacement therapy improves insulin resistance in men with type 2 diabetes and the metabolic syndrome.
- The benefits of conventional cardiovascular risk reduction, and exercise and weight reduction are fundamental to healthy aging and sexual wellbeing for men and women.
- As sexual dysfunction is closely related to metabolic processes and treatments associated with diabetes, it is inevitable that clinicians and specialist nurses will have to address issues around sexuality.

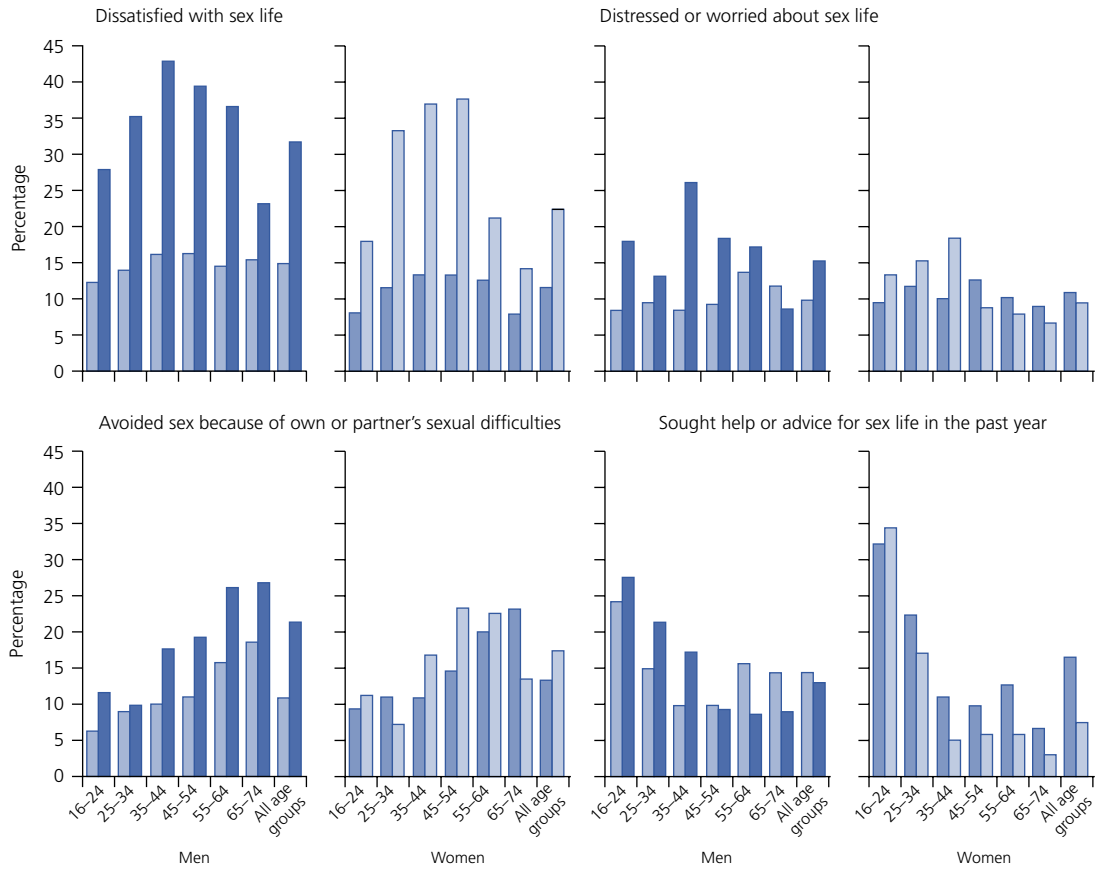
13.1 Why is sexuality important in older age?

As much of primary care management involves the prevention of cardiovascular events, the life expectancy of men has improved considerably over the last 30 years but it still lags an average of 6 years behind women in most European countries [1]. This means that there are approximately three women living beyond the age of 75 for every two men. Patients would ideally like to enjoy a higher quality of life in these additional years, essentially extending the years of middle life rather than senility. Retirement, the removal of financial pressures, and the absence of young adults at home often leads to a phase of sexual freedom and a greater degree of intimacy. Many couples say that in these years their sex lives are better than ever before, but for many, untreated sexual dysfunction associated with diabetes and vascular disease can ruin these important years. Sadly, for some, sexual dysfunction in either or both partners causes relationships to fail, leaving either or both to contemplate new relationships.

13.2 What sexual problems do we see associated with diabetes in aging?

A large Swedish Study reported changes in the over-70 population from 1971 to 2001 and found that 66% of men and 34% of women were still sexually active [2]. The National Survey of Sexual Attitudes and Lifestyles 2013 (NATSAL 3) reported the sexual habits of men and women over 65 [3]. The most common reason why couples cease sexual activity is male erectile dysfunction (ED), which affects over 75% of men with type 2 diabetes over 60 (Figure 13.1) [2–5]. Over 25% of men

Diabetes in Old Age, Fourth Edition. Edited by Alan J. Sinclair, Trisha Dunning, Leocadio Rodríguez Mañas, and Medha Munshi.



		16–24 years		25–34 years		35–44 years		45–54 years		55–64 years		65–74 years		All age groups	
		Unw	W	Unw	W	Unw	W	Unw	W	Unw	W	Unw	W	Unw	W
Men	Sexually active	1291	944	1380	1242	721	1302	639	1204	515	851	326	471	4872	6014
	Sexually inactive	303	200	93	87	62	79	119	150	186	240	271	304	1034	1060
Women	Sexually active	1677	931	2243	1250	1054	1298	877	1197	574	761	286	362	6711	5799
	Sexually inactive	305	177	158	80	113	104	198	186	405	414	506	483	1685	1444

Figure 13.1 UK changes in sexual activity with age (Natsal-3) [3].

and 15% of women over 65 in the UK sought help with sexual problems and similar percentages expressed dissatisfaction with their sex life (Figure 13.2). Not surprisingly levels of dissatisfaction were higher in those not sexually active. The common misconception is that loss of desire in the female leads to cessation of sexual activity but most couples adjust to this and the final straw is the loss of male erection [3, 4]. Assisting patients to overcome sexual problems can be vital to both preserving existing relationships and to establish new relationships vital for long-term care and companionship in older age. Frequently these men would not contemplate a new relationship without the confidence that they will be able to enjoy a full sex life.

The development of drugs to treat ED has markedly increased our knowledge of male sexual function over the last 20 years and this will be reflected in this chapter. The assessments of changes in ED are through well-validated tools such as the International Index of Erectile Function (IIEF) [6], and the patient's appreciation of change is usually quite clear. Aging men also develop delayed or unsatisfactory ejaculation or penile numbness, which is often associated with peripheral neuropathic changes and the use of drugs,

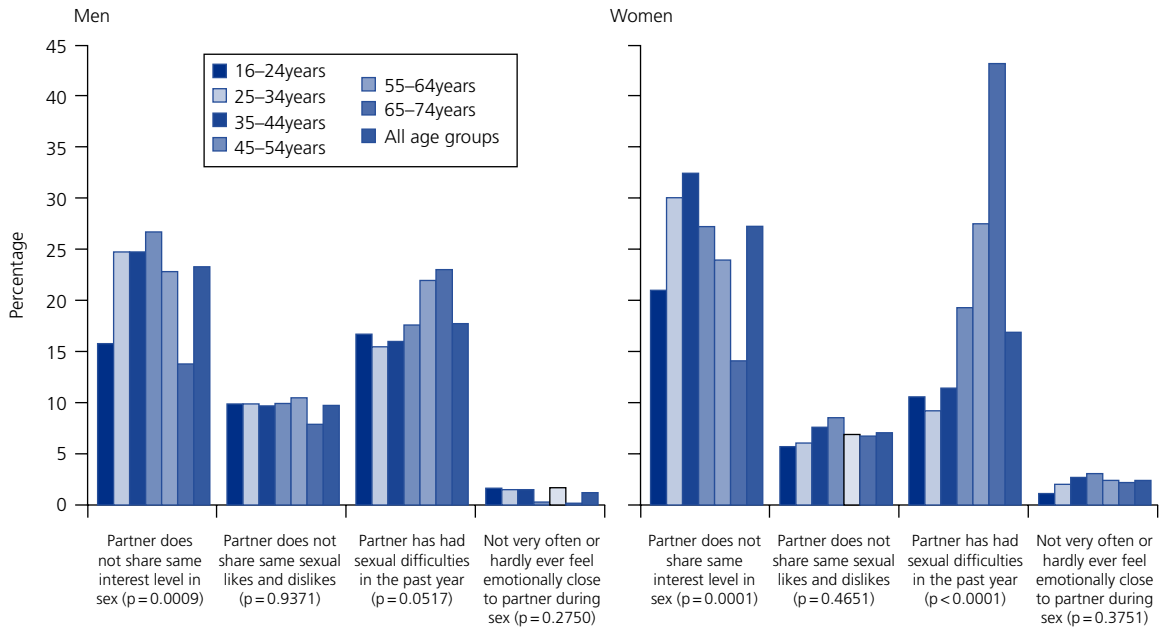


Figure 13.2 Reasons why couples cease sexual activity by age (Natsal-3) [3].

such as α-blockers, to treat associated benign prostatic hypertrophy (BPH) [5].

In the case of women, the problem is often the complex issue of hypoactive sexual desire (HSDD) or low sexual desire, and assessment tools such as the Female Sexual Function Index (FSFI) [7] are highly subjective, leading to great difficulty in establishing true efficacy. Women with diabetes have high rates of depression, which impacts on sexual desire. High prescribing rates of serotonin-selective reuptake inhibitors (SSRIs) antidepressants affect desire, arousal, and orgasm [8]. Vaginal atrophy, associated with the menopause, makes vaginal intercourse painful but is easily treated with vaginal estrogens or water-based lubricants, not oil-based ones such as the commonly used petroleum jelly [8]. Often the man may be referred for erection problems but detailed history from an experienced physician, nurse specialist or therapist detects these coexisting problems that need to be addressed. Physicians concerned with commissioning policies need to more aware that sexual problems may require therapeutic interventions for two people.

The preservation of an active sex life has been shown to be strongly related to longevity in both men and women [9]. In the case of men, survival is related to the frequency of erections and ejaculation, but in women the perceived quality of the sexual relationship was most important [9].

13.3 Impact of aging in men and women

Under the heading of the aging, somewhat different symptoms and complaints are listed by multiple authors [4]. These include:

1. physical changes: increased visceral and abdominal fat, decreased muscle strength, insulin resistance (IR), type 2 diabetes, increasing severity of cardiovascular disease, vegetative or somatoform complaints
2. cognitative complaints: reduced concentration and forgetfulness
3. affective and mood changes: depression, anxiety, tearfulness, irritability and reduced sexual interest
4. behavioral changes, such as reduction in sexual activity or reduced time spent on hobbies once enjoyed
5. psychosocial changes and transitions in aging, such as grown-up children leaving home (“empty nest”), unfulfilled life and career aspirations, ill elderly

relatives, an increase vulnerability to economic changes in the workforce, etc., may culminate in significant distress in the age span 40–60.

From this perspective, negative, age-related stereotypes of physical and mental stress contribute significantly to distress in middle-aged men along with dissatisfaction with their relationship and work. Age-related resources (experience, reflectiveness, caution) are seen as undervalued components of "healthy aging" [4]. A major research problem resides in the fact that the definitions of the aging male are based on clinical samples with a lack of systemic studies in the aging community. The Massachusetts Male Aging Study (MMAS) [10] focused on the associations and impact of erectile dysfunction in an aging population. Betel *et al.* reviewed [4] stratified samples of 2182 men in age groups (18–75) and found a continuous increase in physical, mental, and general fatigue, and a reduction in activity and motivation with age. Exhaustion, cardiovascular problems, and musculoskeletal complaints increased along with reduced health satisfaction and increased depression scores. A marked increase in certain complains was more specific to certain age groups, dissatisfaction with sexuality increased markedly above 60, anxiety was greatest at 60–70 and then improved. Household income and employment were strong associations with anxiety and depression at all ages. The lack of a partner was consistently associated with poor satisfaction with health, particularly over 60.

The European Report on Men's Health 2010 [1] focused on male treatment-seeking behavior at different ages across Europe. Men are low attenders at primary and secondary care services below the age of 45 but over the age of 75 account for significantly greater occupancy of acute hospital beds than women [1]. Such reports have led to greater interest in preventative strategies for men over 40 to reduce the huge secondary care burden created by the aging male population.

13.4 Hormones and aging in men

For over 30 years, physicians have been aware of the importance of multiple hormonal changes with aging, including growth hormone, insulin-like growth factor-1, dehydroepiandrosterone-sulfate, thyroxine, and melatonin. Leptin and sex-hormone binding globulin (SHBG) levels increase with age, and estrogen levels change little with age in men but fall dramatically in women at the menopause [11].

Testosterone levels fall progressively in men from the age of 30 by 1% per annum but low levels are more closely related to obesity [11]. Few primary-care physicians consider measurement of testosterone in men presenting with symptoms such as tiredness, poor concentration, altered mood, depression or erectile dysfunction [11]. This is despite evidence-based guidelines from urology [8, 11] and endocrine societies [12] recommending testosterone measurement as best practice in cases of ED and type 2 diabetes. Androgen therapy has been viewed with suspicion by urologists, often being perceived as quackery. Others have felt that it is inappropriate to interfere with normal aging processes or that we must heed warnings from our enthusiasm for hormone replacement therapy (HRT) in women.

Several terms have been used for the condition of androgen deficiency in aging males, but late onset hypogonadism (LOH) and testosterone deficiency syndrome (TDS) are currently preferred [7]. The term "andropause" is not currently fashionable as it suggests that there is a male equivalent to the female menopause. It can also be described as a biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens. It may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems.

The European Male Aging Study (EMAS) [13] studied 3369 men aged 40–79 at eight European centers and conclude that following three cardinal symptoms were most likely to be related to low levels of testosterone:

- erectile dysfunction
- reduced sexual desire
- loss of morning erections.

Other symptoms such as hot flushes, sweats, tiredness, loss of vitality, reduced shaving frequency, gynecomastia, depressed mood, poor concentration, and sleep disturbance were regarded as less specific.

Recent guidelines suggest that levels of total testosterone (TT) of <8 nmol/l or free testosterone of less than 180 pmol/l require testosterone replacement therapy (TRT) and levels of TT of >12 nmol/l or free testosterone of >225 pmol/l do not. Between these levels a trial of therapy for a minimum of 6 months should be considered based on symptoms [8, 11, 12].

13.4.1 Biochemical assessment of hypogonadism

TT should be measured between the hours of 7 am and 11 am on two occasions at least 1 month apart and ideally be assessed by mass spectrometry (isotope dilution gas chromatography mass spectrometry). Equilibrium dialysis is currently the gold standard for free testosterone as immunoassays based on analogue displacement are currently inaccurate [8, 12]. The European Association of Urology/International Society for Sexual Medicine/British Society for Sexual Medicine (EAU/ISSM/BSSM) management algorithm is now available [11].

13.4.2 Low testosterone and mortality in men

There is increasing evidence that TDS and ED independently predict increased cardiovascular and all-cause mortality [14–21]. Two recent meta-analyses have looked at a large number of long-term studies linking low testosterone to increased cardiovascular and all-cause mortality [22, 23]. Haring *et al.* found that even after strict adjustment for co-morbidities there was a link between mortality risk and testosterone level throughout the studies but that this was not conclusively causal [23]. The authors suggested that TDS associated with aging was a major factor in the gender differences in mortality and that low vitamin D levels independently increased risk [24].

A recent study of 3637 community-dwelling men aged 70–88 in Western Australia [17] showed that low free testosterone and raised SHBG and luteinizing hormone were associated with all-cause and cardiovascular deaths (HR 1.62, 95% CI 18.2–24.8) An earlier study from the same workers [18] studied 3443 men over 70 and showed an increase risk of stroke and TIA associated with minor reductions in total and free testosterone <11.7 nmol/l (HR 1.99) [25].

Muraleedaran *et al.* [26] screened a primary-care diabetic population of 587 patients and followed them up for 5.8 years. They found 475 of men had normal TT levels, 22% were overtly hypogonadal (<8 nmol/l) and 31% were in the borderline range. These percentages were in close agreement with earlier publications by Kapoor [27] *et al.* and Hackett *et al.* [28]. Despite consistent data demonstrating that up to 50% of men with type 2 diabetes will be hypogonadal and that 75% will have ED, with both conditions independently predicting cardiovascular and all-cause mortality [29], it is still not routine practice to screen for low testosterone (and vitamin D) and ED.

13.4.3 The effects of TRT on cardiovascular mortality

A prospective recent study of 587 men with type 2 diabetes [26] involved 5.8 years of follow-up. Low testosterone was defined as TT < 10.4 nmol/l. Fifty-eight men were treated with testosterone for 2 years or more. The mortality rate was 20% in the untreated group, and 9.1% in the normal group independent of co-morbidities and therapies. Mortality was 8.6% in the treated group ($p = 0.049$)

A similar retrospective US study involved 1031 men, with 372 on TRT. The cumulative mortality was 21% in the untreated group versus 10% ($p = 0.001$) in the treated group, with greatest effect in younger men and those with type 2 diabetes [30]. In a recent paper of 145 patients with first ischemic stroke and diabetes, 66% were found to be hypogonadal. In the testosterone-treated group 7% had a recurrence of stroke in 2 years versus 16.6% in the control group, with 28% of the treated men returning to work versus 6% of the control group. There were significant improvements in lipid profile and HbA1c [31].

13.4.4 Effects on angina threshold and heart failure

Men with angiographically proven coronary artery disease (CAD) have significantly lower testosterone levels [32] compared to controls ($p < 0.01$) and there was a significant inverse relationship between the degree of CAD and TT levels ($r = -0.52$, $p < 0.01$) [25].

Studies have shown that pharmacological doses of testosterone can relax coronary arteries when injected intraluminally [33] and produce modest but consistent improvement in exercise-induced angina and reverse-associated ECG changes [34]. The mechanism of action is via blockade of calcium channels with effect of similar magnitude to nifedipine [34].

In men with chronic stable angina pectoris, the ischemic threshold increased after 4 weeks, continuing beyond 12 months [33, 34]. Exercise capacity in men with chronic heart failure increased after 12 weeks [34], predominantly through the improvement in skeletal muscle performance.

13.4.5 Testosterone, IR, and type 2 diabetes

Studies have shown an inverse relationship between serum testosterone and fasting blood glucose and insulin levels [35]. Both hyperinsulinemia and low testosterone have been shown to predict the development of type 2 diabetes [15, 35]. Medications such as chronic analgesics, anticonvulsants, 5-α reductase inhibitors, and androgen ablation therapy are associated with increased risk of testosterone deficiency and IR [11, 12].

Men with IR and type 2 diabetes have increased severity of lower urinary tract symptoms (LUTS) and current evidence favors mechanisms such as IR, pelvic atherosclerosis and inflammation as important factors rather than mere prostate volume [36]. LUTS are strongly associated with ED and long-term studies suggest that TRT may improve LUTS [37]. Phosphodiesterase 5 inhibitors (PDE5Is) are licensed to treat both LUTS and ED, and are more effective with higher levels of serum testosterone [38].

Hypogonadism is a common feature of the metabolic syndrome [39]. Intra-abdominal adiposity (IAA) drives the progression of multiple risk factors directly through the secretion of excess free fatty acids and inflammatory adipokines, and decreased secretion of adiponectin [40]. The presence of excess IAA is an important determinant of cardiometabolic risk. The INTERHEART Study [40] found IAA to be an important predictive factor and recommended waist circumference or hip–waist ratio as a standard measurement of cardiovascular risk. Women with type 2 diabetes or the metabolic syndrome characteristically have low SHBG and high free testosterone [15]. The precise interaction between insulin resistance, visceral adiposity, and hypogonadism is predominantly through increased aromatase production, raised leptin levels, and increase in inflammatory kinins [39].

13.4.6 Lifestyle advice

13.4.6.1 Lifestyle interventions and sexual function in men

Lifestyle interventions have been shown to produce moderate improvement in ED and improve markers of cardiovascular risk in a population of men without signification cardiovascular risk [41]. Exercise training has been shown to improve endothelial function in the coronary and peripheral circulation [42]. Smoking cessation has been shown to reduce incident ED but more importantly to reduce cardiovascular risk by 36% [43]. Intensive exercise and dietary interventions with a Mediterranean diet and reduced calorie intake in a cohort of men without established cardiovascular disease significantly lowered the ejection fraction score by 3 points over 2 years and the response correlated with the degree of weight loss and increased activity [41]. The first step in reducing visceral fat is diet and lifestyle change. Patients should be advised to switch to a low glycemic diet, providing carbohydrate that does not increase glucose levels, which means reducing potatoes and bread, and substituting natural rice and corn [41]. Subjects should be encouraged to combine aerobic exercise with strength training. As muscle increases, glucose will be burned more efficiently and insulin levels will fall. A minimum of 30 minutes of exercise three times weekly should be advised [44].

In a diabetic population, intensive lifestyle intervention failed to produce significant change in IIEF score. These studies suggest that lifestyle intervention is most likely to be effective in mild ED in those without established cardiovascular disease. Wing *et al.* evaluated 1-year changes in erectile function in 306 overweight men with type 2 diabetes from baseline to year one with 8% of men assigned to intensive lifestyle intervention reporting worsening in erectile function compared with 22% of the controls. There was an overall improvement of IIEF score from 17.3 to 18.6 ($p = 0.04$) in the intervention group after adjusting for baseline differences [45].

As improvements in sexual function are modest and take many months, ED medication may need to be combined with lifestyle intervention to produce a satisfactory outcome for most patients. In men with established cardiovascular disease, lifestyle change may reduce cardiovascular risk without improving ED [45]. The likely mechanism is that these patients have established plaque burden that will be less responsive to lifestyle intervention. Significant weight loss, especially associated with bariatric surgery, has been shown to markedly improve testosterone levels and sexual function in men and women [46].

13.4.6.2 Testosterone replacement therapy

In obese males levels of testosterone are reduced in proportion to the degree of obesity. Men with low testosterone levels show less diurnal variation compared with younger men with normal levels [11, 12]. Testosterone increases the levels of fast-twitch muscle fibers [47]. By increasing testosterone, levels of type 2 fibers increase and glucose burning improves.

Weight loss will increase levels of testosterone and augment the effects of lifestyle and exercise. Marked benefits on sexual function (erection, desire, and orgasm) are seen as early as 6 weeks and improvement continues up to and beyond 2 years [48]. Benefits are clear in men with TT < 8 nmol/l whereas patients treated to higher targets showed greater metabolic effects. Patients taking PDE5Is showed greatest improvement, but responses were blunted by co-incident depression [49].

Diabetologists have traditionally considered a low testosterone level to be a consequence of obesity but studies now show that low testosterone can in fact lead to visceral obesity, the metabolic syndrome, and may also be a consequence of obesity [39, 50].

Several large long-term studies have shown that baseline levels of testosterone predict the later development of type 2 diabetes [15, 21, 35].

There is high-level evidence that TRT improves insulin resistance in men with type 2 diabetes and the metabolic syndrome [49, 51–55]. The BLAST study [49] (Table 13.1) suggested that men with depression (23% of the cohort with diabetes) were markedly less responsive across a number of metabolic measures.

Decreases in serum total cholesterol have been noted as early as after 4 weeks [48], but most studies have reported a decrease after 3 months [48]. Greater reductions were seen in obese men [48] with the metabolic syndrome. The decrease in serum triglycerides and LDL cholesterol follows a similar pattern. Studies have found both an increase and decrease in HDL cholesterol [48] dependent on the presence of diabetes or the use of statins. Decline in CRP, IL6 and TNF-α has been consistently reported [55, 56].

13.4.6.3 TRT, weight, BMI and waist circumference

Several studies have shown reduction in waist circumference, visceral fat, and BMI [48, 49, 55, 57]. Preliminary longer-term studies suggest considerable weight loss can be maintained beyond 5 years. A recent 5-year follow-up registry found that a third of men lost over 20% after 5 years and that these losses were progressive and sustained. In some studies a decline in systolic diastolic blood pressure has been observed a decrease in arterial stiffness and a reduction on carotid artery intimal thickness was observed in one study [25].

13.4.6.4 Implications for sexual medicine practice for men

There is a compelling case for asking about ED routinely during male health-related consultation on the basis that ED is a sentinel marker for potential undiagnosed cardiovascular disease [58], particularly in younger men. In men with diabetes, asking about ED has been shown to be a better predictor of future cardiovascular events than hypertension, dyslipidemia, and microalbuminuria [59], and, most importantly, has zero cost. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends annual questioning of all men with diabetes about ED [60] with appropriate investigation, lifestyle advice, and prescribing according to published guidelines. Guidelines consider risk factor modification to be at least as important as intervention therapy [58].

There is strong evidence that patients welcome being asked about ED. In diabetes there is good evidence that sexual problems are strongly associated with depression in both men and women [61]. Sexual dysfunction

Table 13.1 Outcome of therapy with long-acting testosterone undecanoate in a population of men with type 2 diabetes and hypogonadism (BLAST) [68].

	HbA1c (%) >7.5	Weight (kg)	BMI Kg/m2	WC (cm)	TC mmol/l	EF (TT < 8 nmol/l)	AMS (points)	HADS-D	GEQ (% imp)
30 weeks	–0.41	–0.7	–0.3	–2.5	–0.25	+3.0	–5.3	–1.01	46
p value	0.007	0.13	0.01	0.012	0.025	0.006	0.095	0.64	<0.001
82 weeks	–0.89	–2.7	–1.00	–4.2	–0.19	+4.31 +9.57 PDE5I	–8.1	–2.18	67–70
p value	0.009	0.016	0.019	<0.001	0.035	0.003	0.001	0.001	0.0001

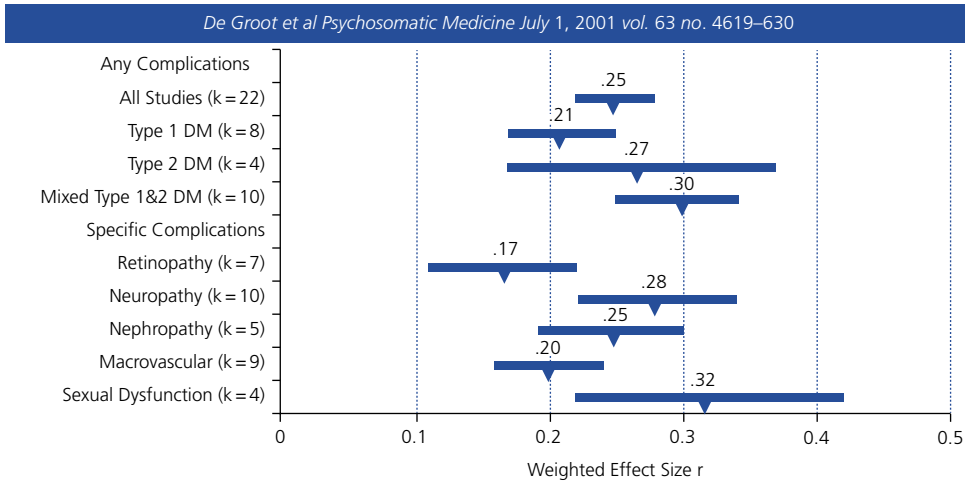


Figure 13.3 Association of depression and diabetes complications: A meta-analysis [62].

has been shown to have a greater impact on wellbeing than retinopathy, neuropathy, and nephropathy (Figure 13.3) [62].

Conventional risk factor assessment in men and women involves the use of tools such as the Framingham Risk Score (FRS) calculator or modifications such as Q Risk to calculate the 10-year risk of myocardial infarction or coronary death [58]. FRS involves age, sex, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, and use of antihypertensive medication. Several important known risk factors are omitted, including family history, diet, exercise, ethnicity, fasting glucose, serum creatinine, serum testosterone, and biomarkers such as C-reactive protein [58]. The FRS is highly focused towards older men where the 10-year risk of an event in absolute terms might be low and the presence of ED might be of greater significance. Araujo reviewed the possible impact of including ED within the risk score tool and concluded that, due to the impact of shared co-morbidities, there might be less impact than expected, particularly with the need to include a quantitative element based on the IIEF and to exclude overtly psychogenic cases. The Princeton III study [58] suggested that increasing the factor of risk by 1.5 for the presence of ED was much in line with the detection of other non-numeric issues such as positive family history or ethnicity, such as afro-Caribbean origin.

13.4.6.5 Implications for pharmacotherapy

Oral therapy with PDE5Is is usually considered first-line therapy for men with diabetes, giving response rates of around 40–65% with currently licensed therapy [63]. Differences in study design and patient selection do not allow for accurate comparison between studies. There is evidence that the addition of at least 2 g of L-arginine can increase the efficacy of PDE5Is [64] and that folic acid supplementation in diabetes improves the response of PDE5Is in animal models [65]. Ciu *et al.* found that the combination of tadalafil 5 mg daily and sildenafil 50 mg on demand was effective in patients with severe ED failing to respond to either on-demand or daily therapy alone [66, 67]. TRT for low testosterone levels (below 8 nmol/l) has been shown to significantly improve ED and desire in men with type 2 diabetes [68] and correcting TT levels of less than 10.4 nmol/l has been shown to salvage patients who previously failed oral therapy [69]. Salvaging PDE5I failures with TRT has considerable cost savings in comparison with second-line therapies [63]. Recent studies suggest that both TRT and PDE5Is are associated with a significant reduction in all-cause mortality [70].

Second-line therapies (intracavernosal injection, alprostadil and vitaros) and combination therapies (used off-label) are more likely to be required for men with type 2 diabetes. Penile implants, although a potentially "curable" option, are usually a less attractive option

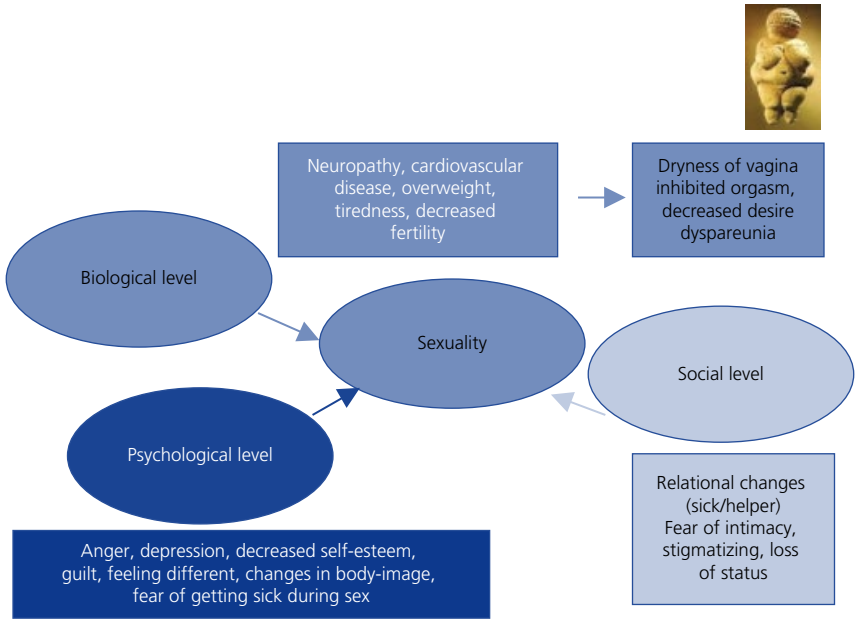


Figure 13.4 Factors related to diabetes which may affect female sexuality.

with advancing age [63]. Older men with diabetes have reduced healing and higher infection rates [63].

Older couples are more likely to be satisfied with a vacuum device and we need to be aware that sexual activity in aging goes beyond penetrative sex [63]. Couples may not be fit enough for sexual intimacy and men may value the return of morning erections to facilitate masturbation if a partner is in poor health. It is often surprising how creative couples can be in such circumstances. It is important that physicians are not embarrassed and are prepared to openly discuss these issues.

13.5 Diabetes and sexuality in women

The full pathogenesis of female sexual dysfunction (FSD) in women with diabetes is complex and studies have been limited by lack of standardized definitions, assessment tools, and sample size. In contrast to men, although the same pathological processes are concerned, the social and psychological issues surrounding diabetes appear to have the greatest impact.

Several studies have shown that female sexual arousal is closely related to the severity and numbers of components of the metabolic syndrome, in a similar fashion to men [71, 72]. Hypertension and dyslipidemia are also strongly associated with reduced arousal (Figure 13.4), presumably through impaired endothelial function resulting in reduced engorgement and lubrication [71]. Just as ED is strongly associated with cardiovascular risk in men, there is strong evidence of a link between cardiovascular disease and sexual arousal in women [71]. In a landmark study, Esposito *et al.* showed that FSFI scores for sexual arousal were significantly lower in diabetes and obesity compared with a control group (Table 13.2) [71].

These findings raise the question as to whether risk factor modification and therapy could result in similar improvements in sexual function for women. Current evidence suggests that this is true but the assessment tools for assessing sexual arousal in women are less robust. An algorithm designed by the European Society for Sexual Medicine (ESSM) to assess sexual problems in women with diabetes is shown in Table 13.3.

There was considerable interest in treating women with sexual arousal disorder with PDE5Is, but results were inconclusive due to the requirement of adequate levels of estrogen and testosterone at a time when HRT received bad press and testosterone supplementation remains unlicensed for women. The conclusion was that, in a subgroup of women with adequate hormone

Table 13.2 FSFI scores in women with diabetes, obesity, and hypothyroidism versus controls [71].

Group diagnosis	1 Diabetes (28)	2 Obesity (39)	3 Hypothyroidism (24)	4 Controls (36)
Desire	3.7 (0.11)	3.6 (0.20)	2.4 (0.21) A, B	4.0 (0.19)
Arousal	3.4 (0.39) A	3.2 (0.32) A	2.8 (0.36) A	5.0 (0.16) A
Lubrication	3.6 (0.46) A	4.0 (0.39) A	3.3 (0.51) A	5.6 (0.11)
Orgasm	3.5 (0.45) A	3.5 (0.37) A	3.2 (0.49) A	5.4 (0.12)A
Satisfaction	3.9 (0.38)	3.8 (0.29) A	3.2 (0.41) A	5.0 (0.12)
Pain	3.7 (0.49) A	4.0 (0.39) A	3.3 (0.53) A	5.3 (0.24)
Global score	21.9 (2.14) A	22.0 (1.82) A	18.2 (2.41) A	30.3 (0.76)

A, $p<0.05$ v 4; B, $p<0.05$ v 2.

Table 13.3 Sexual problems associated with co-morbid conditions in women [72].

Group diagnosis	1 Women with dyslipidemia (441) (SD)	2 Women with normal lipids (115) (SD)	*p* values
Desire	3.9 (1.1)	4.1 (1.2)	0.08
Arousal	3.5 (0.8)	5.2 (1.1)	0.001
Lubrication	3.3 (1.0)	5.1 (0.9) A	0.001
Orgasm	3.5 (1.1)	4.9 (1.1)	0.001
Satisfaction	3.7 (1.1)	5.0 (0.9)	0.001
Pain	4.9 (1.2)	5.1 (1.2)	0.11
Global score	22.8 (6.8)	29.4 (4.9)	<0.001

levels, PDE5Is were effective but that in women with coexisting low desire, then regular dosing might be required [73]. Despite frequent use of PDE5Is, off-label, in women, it is unlikely that large-scale studies will be conducted. One small study suggests that PDE5Is improve insulin resistance in women with the metabolic syndrome and theoretically similar benefits might be expected in endothelial function [74].

13.5.1 Thyroid disease

The prevalence of hypothyroidism in women is consistently 10-fold higher than in men, and is over 20% in women over 70 [71]. Studies suggest that, even in women deemed to be well controlled (TSH < 4 nmol/l) there was a high prevalence of FSD, particularly reduced arousal (Table 13.3). More research is required as to whether tighter control (TSH < 2 nmol/l) might improve sexual function. Hypothyroidism may impair orgasm and desire in women, and men are also particularly prone to either delayed or premature ejaculation in thyroid disease states. Fortunately in men, responses to correction of thyroid status usually reverse the problem.

13.5.2 Depression

Studies have shown consistently that depression is markedly more common in women with type 1 and 2 diabetes and this has the greatest impact on sexual function, particularly low desire [75]. Unfortunately the most commonly used SSRIs antidepressants worsen sexual function, with the exception of mirtazepine, trazadone, bupropion, agomelatine and meclobamide [76]. These are rarely used as first-choice antidepressant

therapies as a sexual history is rarely taken by the GP or psychiatrist before commencing therapy. It is even less common for the patients to report sexual problems before or during therapy. Changing antidepressant can be beneficial but psychiatrists need to balance optimal management of depression with minimal sexual side effects. Occasionally combination therapy and "drug holidays" can be effective. One study showed efficacy for PDE5Is in women with SSRI-induced sexual function [77].

HRT has been shown to improve sexual desire and arousal in women over many years but two recent studies suggesting increased breast cancer risk led to a dramatic fall in prescriptions, to the detriment of the sex lives of many women [78, 79]. Testosterone supplementation has been tried in women with low free testosterone, as testosterone is preferentially bound to SHBG compared with estrogen. A low-dose testosterone patch was licensed for women with surgically induced menopause [80] but this was discontinued for economic reasons. Low-dose testosterone gel at around one-tenth of the male dose can be effective and safe for low desire in women. There are concerns in relation to breast cancer with long-term use [80] and long-term studies are unlikely to be conducted, so most of these interventions for women with remain off-label.

13.5.3 Lifestyle interventions and sexual function in women

Sexual function has been shown to be influenced by a number of lifestyle issues in aging men and women [81, 82]. Esposito found that adherence to a Mediterranean diet in 595 women with type 2 diabetes was associated with the lowest prevalence of FSD based on FSFI. The same authors studied 90 women with the metabolic syndrome assigned to Mediterranean versus standard diet and found improvement in the intervention group [82, 83].

Wing *et al.* in the Look AHEAD study [45] evaluated 375 obese women with type 2 diabetes of whom 229 were sexually active at baseline and 50% of these were found to have sexual dysfunction assessed by FSFI. At baseline, only depression score was related to FSD.

In the cohort randomized to intensive lifestyle intervention (ILI), 83% reported improvements in FSFI scores versus 64% in the diabetes support and education (DSE) cohort ($p<0.008$), with 28% versus 11% at 1 year showing remission of FSD. Corresponding weight loss was 7.6 versus 0.45 kg. ($p<0.001$).

In a recent meta-analysis, Haqq *et al.* [84] concluded that lifestyle (diet and exercise) intervention improves levels of FSH, SHBG, TT, androstenedione, free androgen index, and hirsuitism score in women with polycystic ovary syndrome.

13.5.3.1 Implications for sexual medicine practice for women

Currently there is no evidence to suggest that sex dysfunction in women is a marker for increased cardiovascular risk and therefore there is no basis to justify inclusion as part of cardiovascular risk assessment in current practice. There are no specific guidelines currently available for the treatment of FSD in coronary heart disease and diabetes. Current possibilities for clinical benefit are:

- lifestyle change
- optimal diabetes control
- psychotherapy, especially targeted treatment for depression
- selected (usually unlicensed) medications when appropriate.

The only licensed medication for FSD was a low-dose testosterone patch for surgically induced menopause, but this was withdrawn by the manufacturers for financial reasons. Low-dose testosterone gel is used off-label for women with low desire but low free thyroxine levels in women equate poorly to sexual function scores. PDE5Is have been used empirically in women with variable success due to lower levels of PDE5 expression in women and the need for adequate levels of testosterone and estrogen for adequate desire and lubrication. They are also used for the resolution of psychological (particularly depression) and relationship issues and treatment of associated dysfunction in the partner. SSRI antidepressants carry a high risk of sexual dysfunction, particularly in a high-risk group. Shared management with other specialists may be required to minimize the impact of psychotropic medications.

13.6 Cardiovascular drugs and sexual function in men and women

Cardiovascular medications are usually prescribed by cardiologists and primary-care physicians according to guidelines for the management of the primary condition. Sexual function will rarely have been considered in the

development of these guidelines. The proper treatment of the cardiac condition is of paramount importance and in many cases the sexual physician will have to accept that changes to optimize sexual function may not be possible. In many cases pointing out the importance of sex to the patient and the partner may facilitate adjustment and optimization of therapy. There is level 1a evidence that thiazide diuretics, by increasing angiotensin II levels at endothelial level [85], and β-blockers [86], by multiple central and peripheral actions, are associated with increased risk of developing ED in men and impaired arousal in women with hypertension. Where a β-blocker is clearly indicated, such as post myocardial infarction, nebivolol may be an acceptable alternative as it has been shown to have minor beneficial effects on ED, though it has a weak nitric oxide donor effect [87].

Calcium channel blockers and α-blockers are considered neutral, although early trials with doxazocin suggested mild improvement in ED [63]. More recent studies of tamsulosin suggest a slight worsening on ED with ejaculatory problems, with anejaculation rather than retro-ejaculation in up to 30% [88]. The figure for silodosin approaches 50% [89]. Studies relying on volunteered reporting of sexual side effects significantly underestimate the problem.

ACE inhibitors are considered neutral on erections in men and arousal in women but several studies in men taking valsartan, irbisartan, and losartan showed improvement in all aspects of sexual function, including sexual frequency [90]. One study in women showed improvement in arousal with valsartan. The mechanism is considered to be a reduction in angiotensin II at vascular endothelial levels [91]. The benefits are more likely to be seen in patients with mild hypertension and mild ED as no significance was found between ramipril and telmisartan in the ONTARGET-TRANSCEND study involving men with high burdens of cardiovascular disease [92].

A recent meta-analysis on statins suggested a mild beneficial effect on erections [93], especially in men without established plaque disease, whereas evidence from patients with advanced cardiovascular disease suggests a worsening of erections when statins are added to multi-drug regimens [94]. Simvastatin may produce a reduction in total but not free testosterone and one small study suggested an improvement in erections with a switch from simvastatin to atorvastatin. A recent meta-analysis by Schooling [95] concluded that five small independent studies suggested that the fall in total testosterone with statins was greater in women, although sexual function was not assessed.

13.7 Osteoporosis, frailty, recurrent falls, and muscle strength

The prevalence of osteoporosis in men over 50 is 4–6%, and hypogonadism, particularly with onset in younger men, is an acknowledged risk factor in around 20% of all male cases, with white men at greater risk (7%) than black (5%) or Hispanic American men (3%) [96, 97]. This becomes more important when population data show that by age 75 there are around 60 living men for every 100 living women [1]. The morbidity and mortality of osteoporotic fractures are significantly higher in men than women, although 70% of fractures over 75 occur in women [97].

In terms of both primary and secondary prevention of osteoporosis, men are largely ignored, with the perception being that osteoporotic fracture is almost exclusively a problem in post-menopausal women [97]. Current NICE guidance on osteoporosis concentrates exclusively on women and there is currently no guidance for men, although hypogonadism is frequently quoted as a major risk factor [98]. NICE guidance on prostate cancer [99] does stress the importance of osteoporosis treatment in men on androgen ablation therapy.

A long-term study on the effects of testosterone treatment showed that bone mineral density (BMD) continues to increase in the lumbar spine after 18–30 months of treatment. Meta-regression analysis performed at the lumbar spine and femoral neck revealed a significant effect of TRT, and pooled results from eight randomized clinical trials [100] found that testosterone had a moderate effect on bone resorption markers. No adequately powered trial has yet explored the impact of therapy on hip and vertebral fracture.

Recurrent falls in the elderly are associated with considerable mortality and economic burden. Risk of falling has been shown to be clearly associated with loss of lean muscle, especially in the lower limbs of aging men. Srinas-Shanker *et al.* [101] studied 274 intermediate-frail and frail elderly hypogonadal (mean testosterone 11.1 nmol/l) men aged 65–90 years treated with 25–75 mg testosterone gel or placebo daily for 6 months

and followed up for another 6 months after cessation of therapy. Mean testosterone increased to 18.4 nmol/l at 6 months, and declined to 10.5 nmol/l at 12 months. Isometric knee extension peak torque, lean body mass (plus decreased body fat), and somatic and sexual symptoms improved significantly in the testosterone arm compared to placebo but improvements were seen no more after 6 months testosterone withdrawal. The message is that benefits occur relatively early but treatment must be considered long term.

13.8 Cognitive function

There is evidence that hypogonadism is associated with decreased cognitive function and that testosterone administration enhances performance on spatial cognition and mathematical reasoning [102]. In the MMAS [103], there was no evidence that older age was associated with testosterone in terms of spatial ability, working memory, and speed/attention when adjusted for age and co-variants. However, in the 10-year longitudinal assessment of multiple cognitive domains, higher free testosterone predicted better scores on visual and verbal memory, visual–spatial functioning, visual motor scanning, and a reduced rate of longitudinal decline in visual memory [104]. Studies consistently show that testosterone therapy improves mood, energy, and well-being in younger men, but the effects tend to be less clear in aging men [104]. Nevertheless, benefits are consistently clear in a subset of aging men with manifest low testosterone [105].

13.9 Mood and depression

Symptoms associated with low testosterone are diminished energy, reduced vitality or wellbeing, increased fatigue, depressed mood, impaired cognition, decreased muscle mass and strength, diminished bone density, and anemia. The lifetime prevalence of depression, at 24%, is known to be three times higher in type 2 diabetes than the general population and the most commonly cited reason is the burden of co-morbidities in diabetes [106]. None of the papers reviewed in a meta-analysis of 42 studies in 200,145 subjects considered androgen status, despite the obvious overlap in symptoms between hypogonadism and depression. Diabetes was found to be a greater risk factor for depression in male than in female type 2 diabetes and sexual problems were the complication most associated with depression [61, 62].

A. randomized placebo-controlled study of long-acting testosterone undecanoate for 30 weeks on 184 men with the metabolic syndrome or type 2 diabetes (mean age 52 and mean baseline testosterone of 8 nmol/l) showed significant improvements in Beck Inventory scores for testosterone versus placebo of 2.5 points and 7.4 points on the aging male score, as well as 3-point improvements on the IIEF [107]. Although low testosterone has been shown to predict incident depression in aging men, only two of nine randomized clinical trials have shown a significant improvement in depression scores in a general population of aging men compared with placebo [106]. Combined therapy with antidepressants has been shown to be superior to antidepressant plus placebo in a group of younger men with refractory depression [108].

13.10 Testosterone and Alzheimer's disease

Men are relatively protected from Alzheimer's disease compared with women. There is evidence that androgens confer protection from Alzheimer's disease in their own right and a recent study found a link between cognitive functioning and bioavailable testosterone [109, 110]. Testosterone therapy has been shown to improve mood and quality of life in men with Alzheimer's disease despite cognitive improvement failing to reach clinical significance. The conclusion from these studies is that free testosterone should be monitored in cases of Alzheimer's disease and a therapeutic trial may be appropriate in many cases [111].

13.11 Testosterone and quality of life

Several studies have shown improvement in aging male symptom scores with testosterone therapy but the validity of these findings has been questioned in patients with chronic illness. Validated quality of life tools such as SF12 and SF36 have shown significant improvements in physical and mental health scores in general

populations of aging men both with and without diabetes [112]. In the BLAST diabetes study at 12–18 months nearly 70% of mean (men age 62) stated that testosterone therapy had improved their health and 38% stated that improvement was definite (Table 13.1) [68].

13.12 Long-term safety of testosterone therapy

A meta-analysis of 1000 patient years versus placebo suggests a slight reduction in myocardial infarction and CVA but a marked reduction in coronary interventions [113]. Two recent US studies showed a slight increase in mortality taking TRT [26, 114]. Several recent US studies have shown conflicting results: a retrospective study showing a reduction in events with TRT, and two studies showing a slight increase in mortality with TRT [115–117]. These latter two studies appear to be flawed in their methodology and statistical assessment, resulting in heavy criticism and demands for retraction. Current EAU, ISSAM and BSSM guidance, endorsed by multiple meta-analyses [113, 118–120], is that there is "no evidence TRT is associated with increased risk of prostate cancer or activation of subclinical cancer".

Most reviews conclude that sufficiently powered long-term studies are needed. For logistical and ethical reasons, the ideal long-term study is unlikely to be done and until then physicians will have to practice on best available evidence.

13.13 Effects of androgen ablation therapy

Men with prostate cancer treated with androgen deprivation develop an increase in fat mass with an altered lipid profile, increasing total LDL, HDL, and triglycerides by 9%, 7%, 11% and 26.5% respectively. These patients also appear to develop insulin resistance, hyperinsulinemia, and hyperglycemia. The risks of diabetes mellitus increase by 44% and mortality of cardiovascular diseases by 16% during a follow-up of up to 10 years [80]. The authors concluded that before commencing androgen deprivation treatment, the overall health, co-morbidities, and life expectancy of the patient need to be fully assessed [121].

13.14 Conclusions

The benefits of conventional cardiovascular risk reduction, and exercise and weight reduction are fundamental to healthy aging and sexual wellbeing for men and women. There are considerable health benefits associated with continued sexual activity in old age. Sexual problems are common in men and women with type 2 diabetes but research has concentrated on male problems and therapeutic options for women are limited, as is the availability of licensed therapies.

There is considerable evidence of modest cardiac and metabolic benefits plus sexual, mood, and quality of life changes associated with TRT for men, which together may add up to substantial benefits for many patients. These may potentially be denied to patients by fears over prostate risk that are not currently supported by evidence. There are emerging data of the benefits of continued sexual activity into old age and even that oral drugs used to treat erectile function may improve survival. Ideally, we need large long-term studies to resolve these issues with certainty but such studies are unlikely to be done for logistical and financial reasons. Until then patients require advice and treatment based on current best evidence.

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CHAPTER 14

eHealth and diabetes: Designing a novel system for remotely monitoring older adults with type 2 diabetes

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KEY MESSAGES

- The growth in smartphone adoption and widespread data connectivity has democratized access to digital services across the world.
- The use and clinical impact of any mobile phone application for the management of health is particularly complicated in the case of older adults due to practical aspects such as the poor usability of most applications and the limited amount of co-morbidities that can be addressed with a standalone, disease-specific application.
- By mid-2014 there were more than 1100 iOS and Android-specific diabetes apps available in the Apple App Store and Google Play.
- In one study, 65% of the analyzed apps included tools for tracking insulin or other medication, approximately 50% of the applications had some form of diet management, while approximately 40% included some kind of motivation and monitoring of physical activity and weight tracking.
- A novel approach is needed for properly managing older patients based on the following premises: overall quality of life, functional status, involvement of informal caregivers and health professionals in the healthcare process, built using usability and accessibility standards, providing patients and informal caregivers with a smooth, non-invasive experience and professionals with a tool that facilitates their daily work.

14.1 Introduction

Over the last 15 years, global internet usage has increased almost seven-fold, bumping the figures up to 3.2 billion worldwide users in 2015 (43% of the overall population) [1]. Moreover, the use of intelligent mobile devices, such as smartphones and tablets, has increased dramatically during the last decade: the number of unique subscribers to a mobile line has increased from over 1 billion in 2003 (1 in 6 people worldwide) to 7 billion in 2015 (reaching a penetration rate of 97% of the overall population). In terms of connectivity, in 2015 approximately 69% of the population used 3G coverage; it is expected that by 2020 there will be 3732 million mobile devices with a 3G connection and 2284 million with a 4G connection [2]. In consequence, the growth in smartphone adoption and widespread data connectivity has democratized access to digital services across the world. One of the fields where the use of mobile technologies is expected to produce a greater impact is the development of ICT-based health services, namely electronic health (eHealth) and mobile health (mHealth) services.

Despite the maturity of the technology and the availability of devices and data connections, no mHealth initiatives have been reported to be fully integrated into

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routine medical practice within any relevant national health system. Some examples of small- to medium-scale pilots can be found in the literature (i.e., the DiabMemory initative in Austria [3] and others). On the other hand, a market that has flourished remarkably within the last years has been the development of mobile applications (thereafter apps) for the self-management of health. These apps are highly disease-centered and are usually not integrated with any general-use personal health record (PHR). Moreover, the use and the clinical impact of any mobile phone app for the management of health is specially complicated in the case of older adults due to practical aspects such as their poor usability and the number of co-morbidities that cannot be addressed with a standalone, disease-specific app.

This chapter analyses the current state of the art in the field of mobile apps for managing diabetes. It then focuses on the problems that have prevented these apps from reaching a broad audience. Finally, a novel approach for using mobile technologies to remotely manage the health status of older adults with diabetes, which can be easily extended to other chronic conditions, is proposed.

14.2 An overview of ICT solutions for managing chronic conditions

eHealth lies in the "intersection of medical informatics, public health and business; referring to health services and information delivered or enhanced through the Internet and related technologies" [4]. The term refers to a way of thinking, an attitude, and a commitment for networked, global thinking to improve health care locally, regionally, and worldwide by using information and communication technology (ICT).

Mobile health (hereafter mHealth) is a component of eHealth. No standardized definition of mHealth has been established yet. One of the most cited definitions of mHealth is the one provided by Istepanian *et al.* [5], who defined mHealth as "emerging mobile communications and network technologies for healthcare". In 2011, The World Health Organization (WHO) proposed a broader definition that included also sensors as part of the mHealth paradigm, as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [6].

According to the WHO [6], the four most frequently reported mHealth initiatives worldwide are (1) health-care centers, (2) emergency toll-free telephone services, (3) managing emergencies and disasters, and (4) mobile telemedicine. Whilst many examples of production-level initiatives can be found in the three first categories, most mobile telemedicine initiatives reported were in the pilot or informal stages, and hence are not integrated into the routine clinical practice.

In this sense, European-funded projects such as METABO and Reaction (FP7-248590) have designed, developed, and tested integrated systems for the remote management of diabetes based on the management of disease-related parameters such as glucose levels and weight, and therapy management covering aspects such as diet and physical exercise, among others. Most of these projects adopted a closed-loop approach, comprising three main modules: (i) a user station comprising a mobile device (PDA or smartphone) for data acquisition and feedback provision, and a set of sensors for acquiring data about relevant biometric parameters (glycemic level, weight, etc.), (ii) an intelligent back-end, which stores and processes all data gathered by the user station, and (iii) a professional station that allows health professionals to remotely manage the health status of the patient. Although these projects have demonstrated moderate to good results in terms both of clinical outcomes and improvement of self-management [7, 8], none of these systems has been able to "tramp the last mile" and finally be integrated into routine clinical practice.

From an industry standpoint, mainstream companies such as Apple, Cisco, and Microsoft have developed proprietary health repositories connected to proprietary devices and sensors. Nevertheless, this vendor-locked approach might prevent these solutions from being used in public national health systems. On the other hand, non-profit organizations such as Co4Salut and Tidepool (http://tidepool.org/platform/) are working on the development of open source platforms for storing and sharing medical data. Nevertheless, it seems unlikely that a public health system will rely on such solutions at the time being.

Besides integrated telemedicine apps, one market that has flourished in the last few years within the field of mHealth is mobile apps for the personal management of health. From late 2011 to early 2014 the number of mHealth apps that were published on the two leading

platforms, iOS and Android, more than doubled to more than 100,000. In general, mHealth apps predominantly target chronically ill patients (31%) and health- and fitness-interested people (28%). On the other hand, only 14% of health apps are targeted to physicians.

According to *Diabetes App Market 2014*, issued by research2guidance [9], by mid-2014 there were more than 1100 iOS- and Android-specific diabetes apps available in Appe's App Store and Google's Play Market. These results show a growing trend in the availability of diabetes-related apps for the most common mobile operative systems, for example Chomutare *et al.* [10] report an increase from 60 diabetes-related iPhone apps in July 2009 to 260 in February 2011.

Nevertheless, by 2013, only 1.2% of the overall target group (people with diabetes, 20–79 years, who have a smartphone or tablet) used any mobile apps to manage their health status [9]. This report foresees that the market penetration of diabetes management apps will grow to 7.8% by 2018. Taking into account that patients diagnosed with diabetes experience a remarkable decrease in their quality of life, and given that mobile technologies could provide great help in managing all life-changing aspects that come with diabetes (diet management, physical exercise, etc.), it should be further analyzed why diabetes apps have failed to gain high market penetration. The following section presents some studies that have conducted a thorough analysis of the available diabetes management apps, and the subsequent section proposes a novel approach for using mHealth to help older adults with diabetes manage their health status.

14.3 Diabetes management apps: strengths and weaknesses

As mentioned in the previous section, according to research2guidance [9], by mid-2014 there were more than 1100 iOS and Android specific diabetes apps available in the Apple App Store and Google Play. Nevertheless, by 2013 only 1.2% of the overall target group (people with diabetes between 20 and 79 years old who have a smartphone and tablet) regularly used an app to manage their condition.

In 2011, Chomutare *et al.* [10] analyzed 137 diabetes management apps available in the Apple Store and Google Play markets. This study provided a classification of these apps based on the functionalities: 33% of the apps implemented some form of health tracking (blood glucose, insulin doses, carbohydrates, weight and physical activity), 22% provided training or education on diabetes management, 8% were reference food databases, 5% were social networks or forums, and approximately 8% were dedicated to the healthcare provider. Regarding data warehousing, only 29% of the apps provided data synchronization with PHRs or web portals. Regarding education and motivation, only 7 out of the 27 apps with an educational module had personalized education, tips, feedback or advice. Some form of lightweight integration with social media was present in 15% of the apps, while 12% had disease-related reminders.

On the other hand, Joyce [11] selected the most relevant iPhone apps available and analyzed the most common functionalities. According to this study, 65% of the analyzed apps included tools for tracking insulin or other medication, approximately 50% had some form of diet management, while approximately 40% included some kind of motivation and monitoring of physical activity and weight tracking. This represents an enormous effort by Apple to include diabetic patient management tools within its iWatch technology. A similar study with Android applications carried out in 2012 analyzed 42 unique apps for managing diabetes with Android phones. In total, 86% of the apps included tools for self-managing blood glucose levels, 45% a tool to track insulin or oral diabetic medications, and 26% a prandial insulin dose calculator; regarding other parameters, 69% of the apps allowed users to track their weight or blood pressure [12].

Nevertheless, most of the diabetes-related apps in both operating systems only combine one or two of the aforementioned functionalities. In a systematic review carried out by Arnhold *et al.* [13], the authors state that 54% out of 656 analyzed apps offered just one functionality. As a result, most of these apps are not suitable for providing patients with diabetes with holistic care that addresses all aspects of their condition.

Another relevant factor that may prevent users from adopting mHealth solutions to manage their condition is their lack of usability and accessibility of apps. This can be especially relevant in the case of older users, who are usually less technology savvy and may develop different degrees of disability (from short-sighted to blindness, from hard of hearing to deaf, etc.) that may prevent

them from using an app. Demidowich *et al.* [12] carried out a usability study of 42 diabetes-related apps, reaching a mean composite usability score of 11.3 out of a possible 30.0. This study concluded that few apps were sensitive to the age and gender of the users. Arnhold *et al.* [13] performed an evaluation of the usability of 66 diabetes apps (29 for iOS, 28 for Android, and 9 for both), reaching an average value of 3.0 to 4.0, meaning good to moderate usability. One of the most criticized aspects in both studies was the lack of functionalities in most apps. However, in general multifunctional apps performed considerably worst in terms of usability. Most of the apps (approximately 1% in iOS and 5% in Android) were not connected to any external measuring device, forcing users to manually enter a remarkable amount of data, which may prevent long-term engagement.

Another relevant factor that may compromise the mainstream use of these apps is that, in most cases, they are not based on clinical standards. Most of the apps that provide patients with educational content do not generate any personalized content (i.e. recommendations on physical activity and/or nutrition, etc.) based on the status of the patient. As an example of this lack of medical relevance, it is worth mentioning that, at present, only one diabetes management app – WellDoc (http://www.mobilehealthglobal.com/showroom/catalogue/apps/167/welldoc-diabetes-manager-system) – has been certified as a medical device by the US Food and Drug Administration.

It can be concluded that mHealth platforms and apps have huge market potential, but most of the state-of-the-art developments fail to provide a holistic care approach for the following reasons:

1 There is a lack of medical evidence in commercially available apps. Most apps function mainly as data collectors and visualizers, providing only generic advice on how to cope with the disease. Indeed, most of the apps focus on one or two biometric parameters (i.e. glucose, weight), disregarding complex cases and other co-morbidities.
2 They have a small number of functionalities, which prevents these systems and apps providing a holistic approach, hence excluding complex patients suffering from other co-morbidities.
3 They have poor usability and accessibility. Most of the apps and devices do not have a connection to a measuring device, forcing users to manually enter their data. In some cases users need to input their data 6 to 12 times per day, making the experience invasive and cumbersome.
4 There is a lack of personalization of the educational content. Roughly 25% of the available apps provide personalized tips and educational content. Personalization in these cases is only based on the evolution of the biometric data, disregarding aspects such as age and gender considerations.
5 There is a lack of involvement of the other stakeholders involved (informal caregivers, etc.). Most systems and apps are dedicated to promote self-managing of diabetes, providing people with diabetes with tools for self-assessing their status. These systems and apps do not include functionalities for including informal caregivers or health professionals in the loop.
6 There is a lack of integration with current health information systems. Only a small fraction of the available apps are connected to a PHR. The repositories are usually proprietary and not connected to national or regional health information system.

All of these drawbacks are especially significant when developing systems and apps for managing diabetes in older people. The following section presents a novel approach for managing diabetes in older people, shifting the focus from symptoms and biometric parameters to function improvement and well-being enhancement.

14.4 Diabetes and older people: looking for a novel approach

More than 25% of people over 65 have diabetes and approximately 50% have pre-diabetes [14], which represents 35% of diabetes prevalence in adults, most of whom have type 2 diabetes mellitus (T2DM). Over a 10-year period (1994–2004), the annual incidence of diabetes increased by 23% and prevalence increased by 62% in those aged 65 years and over [15].

An aging population proportionately increases the health impact on a society because of increased numbers and more years lived with disability. Diabetes exacerbates this burden: it is ranked as the seventh and eighth cause of years of life lost and disability-adjusted life years (DALYs), respectively in western societies and the 14th cause globally in the ranking of causes of DALYs [16], accounting for 1.9% of total DALYs (an increase of more than 60% in 2010 compared with data

obtained in 1990). The predicted increase in diabetes prevalence is mainly due to increased numbers of older people [17].

Diabetes mellitus (DM) is among those chronic diseases associated with an increased risk of developing frailty and a poor evolution from frailty to disability and other adverse health outcomes in older people. Diabetes has been previously suggested to be a model of frailty and significantly increases the risk of frailty (odds ratio (OR) 1.18–1.27) [18], mobility disability (OR 1.71), instrumental ADL (IADL) disability (OR 1.65) and activities of daily living (ADL) disability (OR 1.82) [19, 20].

Diabetes may explain up to 20% of the excess risk of disability in an elderly population [21–23], with an annual increase in the risk of developing any disability around 100%. However, the classical diabetic co-morbidities only explain 38% of the excess risk in women and a disappointing 16% in men [24]. In recent studies involving older people, up to 28% of those with diabetes required some help with activities of daily living (compared with 16% in those without diabetes) and this functional decline can only be explained in half of the cases by the classical complications of the disease. This worsening in functional status, added to the increased medical co-morbidities/overmedication associated with diabetes, results in many older frail people becoming more disabled and exhibiting an impaired quality of life associated with rising health care resources [25].

It therefore seems clear that classic, disease-based approaches are not optimal for managing diabetes in older adults. Diabetes management strategies for high-functioning older people with diabetes with a long life expectancy are similar to those for younger people but such strategies are unlikely to be safe for those who are pre-frail, frail or have disabilities. As an example of best practice in a disease-based approach Chomutare *et al.* [10] defined a set of features (in random order) as important variables for diabetes self-management, in order to comply with clinical guidelines:

1 education and personalized feedback
2 diet management
3 weight management
4 physical activity
5 communication and patient monitoring by primary care providers
6 insulin and medication management
7 other therapies (foot, eye care)
8 psychosocial care
9 immunization.

Nevertheless, this disease-based approach – based on clinical guidelines – does not include any aspects of functional assessment or personalization for the management of the health condition of older adults. In this regard several recent documents have put the emphasis in the management of these patients on their functional status [26–28], fitting the different components of the treatment (physical exercise, nutrition, clinical targets, and drug treatment) to their functional condition. Hence, an aim should be to develop a proactive risk minimization care plan that suits the individual's functional status, optimizes quality of life, maintains independence for as long as possible and enables a dignified death [29]. To achieve this, three main factors should be considered which are related, respectively, to the patient, the disease, and the therapeutic options provided by the healthcare system and its facilities, as presented in Figure 14.1.

Disability and frailty modulate the type of care that is needed in older people, with different therapeutic targets. Moreover, the characteristics of a growing sector of the population in the 21st century (chronic disease, co-morbidity, changing needs of care depending on different care pathways, impact on functional status) have changed the principles on which the models of health care should be built. In contrast to the healthcare systems of the previous century, where the main activity for older people was focused on acute episodes of disease, the modern approach for healthcare systems should be centered around providing a system of care based on four main principles: integrated, coordinated and continued care plus an involvement of the patient in the provision of his/her care (self-empowerment). However, at present, we do not have well-defined models of care for these patients and few of them have been tested. This is also the case for ICT systems and platforms.

Three main components must be embraced in any healthcare system designed to meet the needs of these patients:

1 A multimodal approach, embracing the different components of care required by these patients: education about the disease and their functional condition (from robustness to disability), nutritional and exercise advice and counselling, medicines management, including testing treatment adherence,

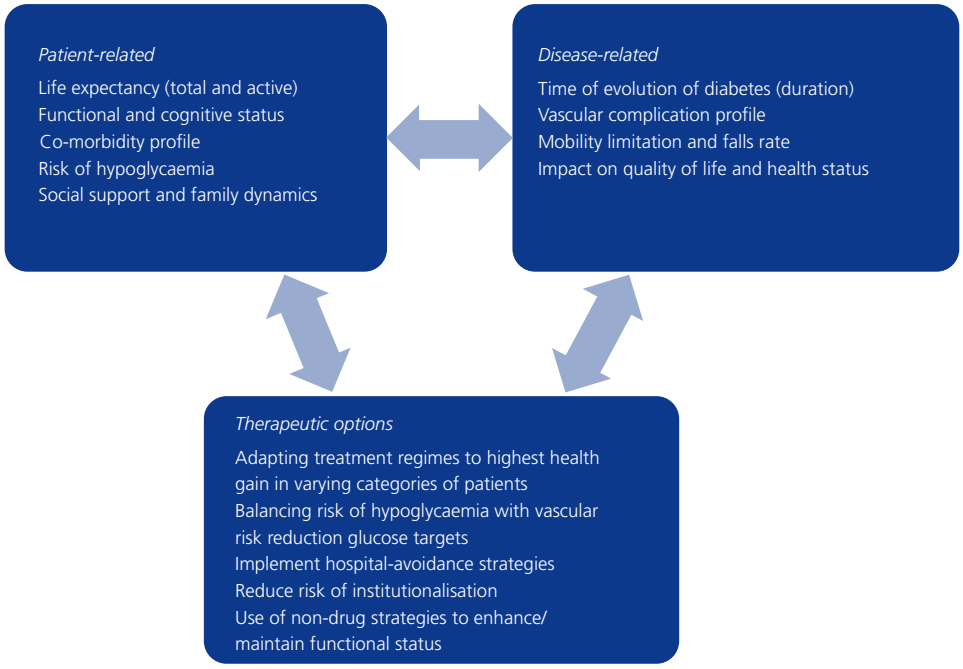

Figure 14.1 Factors involved in clinical decision-making for older people with diabetes with therapeutic options.

and functional and cognitive monitoring made easy for self-management.

2 Involvement of the informal caregiver, who is someone involved in various aspects of clinical and social care of around 50% of people older than 70 years with chronic disease [30]. Recently, the UK National Institute for Health and Clinical Excellence (NICE) acknowledged that diabetes is "[…] predominantly managed by the person with diabetes and/or by their carer as part of their daily life" [31]. The most frequent helpful tasks undertaken by the primary carer include "Help with diet" (48%), "Help with medication" (22%) and "General support" (15%) [32, 33]. More information about these tasks and acquiring the right skills and expertise to provide the care are the most common requests of caregivers.

3 The formal caregiver: those paid professionals who are involved in patient care. One of the basic pillars of care for frail/pre-frail/disabled older people with chronic disease is the professional network, including both specialized care (geriatricians, cardiologists, endocrinologists, nurses, physiotherapist, dieticians, etc.), which is usually hospital-based, and primary care [34]. Thus, the connectivity among them and with the patient and his/her informal carer is a basic requirement for providing appropriate continued and coordinated care.

These characteristics raise the necessity of developing and implementing models of care tailored to the needs of patients that overcome the limitations of the usual models based on the control of the classical targets (metabolic, vascular, neurological, etc.) of the disease to focus on a new "functional model" to manage both frailty/disability and chronic disease using an interdisciplinary approach to delay or impede the onset of frailty and its progression to disability. This model stems from the following principles (available at http://ec.europa.eu/research/innovation-union/pdf/active-healthy-ageing/20120403_diabetes.pdf):

- It should be focused on the patient and their functional status/quality of life.
- It should bridge cultural/ethnic boundaries.
- It should bridge physical boundaries, making the relationship between the patient and health providers easy and friendly.
- It should use information systems that are sustained by ICT support systems, eHealth clinical care approaches and internet-linked clinical support models.

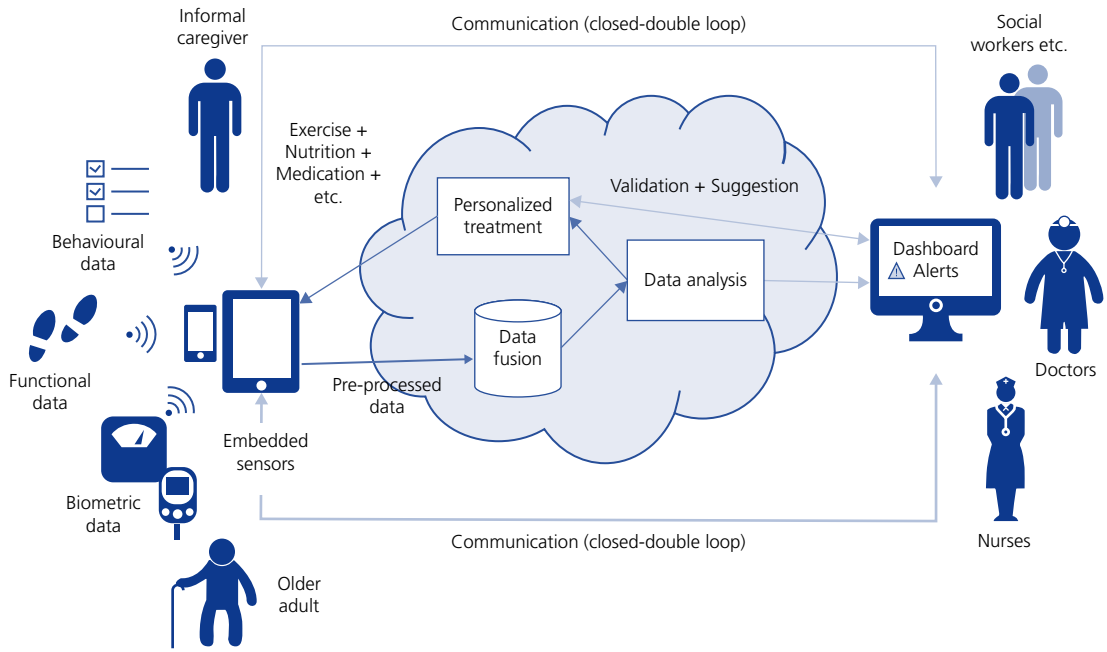

Figure 14.2 Proposed architecture for remotely managing older adults with diabetes.

- It should provide carer involvement strategies and cost-effective patient care by well-motivated and trained healthcare personnel.

Figure 14.2 proposes an architecture for a mobile-based ICT system that aims to implement the aforementioned principles, hence providing older adults with diabetes with integrated care. This system aims to go one step further by developing holistic and preventative models oriented to detect functional and cognitive decline and to provide a holistic approach to the patient and their caregivers.

The proposed system has the following characteristics:

- Data acquisition: The system uses both external and embedded sensors to acquire relevant information about the patient. Regular eHealth and mHealth platforms gather mostly disease-related data (i.e. glucose levels in the case of patients with diabetes), disregarding any data about the functional or cognitive status of the patient. The proposed system would gather the following levels of data:
  - Functional data not directly related to the disease that provide information about the overall functional capacity of the patient. Relevant functional data include aspects such as gait speed, gait variability, and muscle strength, and provide a good overview of the level of independence and quality of life of the patient.
  - Behavioral data related to the routine activities of the user that provide physicians with information about daily activities (such as nutritional habits, medication adherence, etc.) and social activities. Behavioral data are closely related to the functional status of the patient.
  - Biometric data related to specific, disease-related parameters that might have an influence on the functional status and hence the quality of life of the patient. In the case of diabetes, biometric data include parameters such as glucose levels, HbA1c, etc. Unlike common eHealth and mHealth solutions, biometric data are considered as complementary data, basically providing insight into the influence that the disease would have on the functional status of the patient. The system would therefore be easy to extend to monitor relevant parameters for older adults suffering from other chronic diseases or co-morbidities, such as heart failure or chronic obstructive pulmonary disease.

- Data analysis: The system will gather, store, and analyze all data to estimate the functional status of the patient. The system will implement machine-learning and/or smart data algorithms able to detect any positive or negative trends and/or generate alerts in case any anomalies are detected.
- Treatment recommendations: The system will implement a rule-based system, based on clinical evidence, that will provide patients with personalized treatments and recommendations based on their functional and clinical status. The system will provide recommendations on physical activity, nutrition, and daily life and social activities.
- The system will implement a closed double-loop system, allowing communication between healthcare providers, patients, and informal caregivers. The system should foster the involvement of informal caregivers in the care of their loved ones.
- From a professional standpoint, the system will provide formal (health) carers with the diagnostic and monitoring instruments to provide the best diagnostic, monitoring and therapeutic instruments to provide the best care, thus contributing to improving the quality of life for the individual and their caregiver, including end-of-life care.

To sum up, the system proposed in this chapter would improve on current healthcare models by overcoming the traditional disease-centered approach and putting the focus on one of the main health-related problems of the older people (disability) and its main risk factor (frailty). Indeed, international organizations such as the International Diabetes Federation, among many others [35], have strongly supported this approach. Our proposed system aims to facilitate the procurement of integrated, coordinated, and continued care in which all the stakeholders involved (formal and informal caregivers, and the patient) are part of a network of care.

14.5 Conclusion

The widespread adoption of mobile devices and the rapid advances in ICT technologies provide a great opportunity for developing systems and apps for empowering citizens to take better care of their own health status. Within the few years, several apps and systems have been developed for managing chronic conditions, such as heart failure and diabetes. The growth in the number of apps available for self-managing diabetes has been especially remarkable, as its potential market share and the characteristics of the target audience group (covering a wide range of ages) provide a great opportunity for long-term improvement and commercialization. Nevertheless, most of the systems available at the moment have failed to be widely adopted for several reasons, such as their lack of functionality, their poor usability, and their disregard of clinical best practices. This is especially relevant in the case of older adults with diabetes, who usually suffer from other conditions and co-morbidities, and who encounter more difficulties in using technologies. A novel approach is needed for properly managing this kind of patient based on the following premises:

1. The management approach should be based on the overall quality of life of the patients and on their functional status, overcoming the traditional disease-centered approach. Most older patients with diabetes suffer from other conditions that, in the end, affect their independence and hinder their quality of life. The proposed system should help older adults track their diabetes, viewing it as another factor for provoking functional and cognitive decline, instead of considering to be the main indicator of their health condition.
2. The approach should involve informal caregivers and health professionals in the health care of the patients. In the case of older patients, informal caregivers carry the weight of the healthcare process in many cases, but are excluded from the communication loop by most systems. In order to ensure proper care, they should be included in the process.
3. The approach should be built using usability and accessibility standards, providing patients and informal caregivers with a smooth, non-invasive experience, and professionals with a tool that facilitates their daily work.

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SECTION C

Treatment and care issues

CHAPTER 15

Insulin resistance and the metabolic syndrome

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KEY MESSAGES

- The metabolic – or insulin resistance – syndrome is a constellation of cardiometabolic risk factors that tend to cluster together in affected individuals more often than predicted by chance.
- The presence of the metabolic syndrome substantially increases the risk of developing type 2 diabetes and cardiovascular disease, and is associated with a range of adverse clinical outcomes, many of which are closely associated with aging.
- The metabolic syndrome is largely asymptomatic. Diagnosis rests on the presence of clinical and biochemical components. Insulin resistance, which is difficult to measure outside the setting of clinical research, is not included in the diagnostic criteria.
- Current estimates suggest that approximately 20–25% of the world's population is affected by the metabolic syndrome. The prevalence of the metabolic syndrome rises with age. More than 45% of people aged >60 years have the metabolic syndrome.
- Obesity – particularly of central or visceral distribution and with ectopic fat deposition in the liver – is a core feature of the metabolic syndrome. Subclinical vascular defects include impaired endothelial function and arterial stiffness.
- The global increase in the metabolic syndrome has attributed to population expansion and aging in concert with increasing levels of obesity, unhealthy diets, and sedentary lifestyles. Certain drugs may predispose to the development of the metabolic syndrome.
- Prevention and treatment are grounded in lifestyle modifications, that is, decreased calorie intake and increased levels of physical activity. Adherence to the variants of the Mediterranean diet is associated with an increased probability of regression of the metabolic syndrome.
- Medication may be required to control blood glucose, blood pressure, and blood lipids. In high-risk subjects, lifestyle changes may be more effective than pharmacotherapy; no drugs are approved for the prevention of diabetes in individuals with the metabolic syndrome. Anti-obesity drugs may be useful and bariatric surgery is effective in ameliorating the risk factors that comprise the metabolic syndrome.

15.1 Introduction

Insulin resistance may be usefully defined as a state in which normal concentrations of insulin produce a less than normal biological response [1]. Impaired insulin action is a feature of an extensive list of physiological and pathological conditions, many of which are age dependent (Table 15.1) [2]. Metabolic syndrome is also known as the insulin resistance syndrome (or syndrome X) in recognition of the pivotal pathogenic role of impaired insulin action [3]. Insulin resistance is a putative biomarker of disease and disability in older people [4].

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Table 15.1 Physiological and pathological states associated with whole-body insulin resistance.

Physiological states
Adolescence
Pregnancy (second and third trimesters)
Luteal phase of the menstrual cycle
Post-menopause[a]
Aging[a]
Common pathological conditions
Obesity[b]
Glucose intolerance
Type 2 diabetes
Metabolic syndrome[c]
Sedentary lifestyle (vs regular physical activity)
Non-alcoholic fatty liver disease/steatohepatitis

[a] The evidence for direct effects of these physiological processes on insulin sensitivity is inconsistent. Changes in body composition and other factors may, at least in part, explain the reduced insulin action reported in some studies.
[b] Includes lesser degrees of overweight. Abdominal adiposity is more closely associated with whole-body insulin resistance than gynecoid subcutaneous fat deposition. Ethnicity is an important modifier of the metabolic effects of adiposity; non-white populations, including East and South Asians, develop adverse cardiometabolic profiles at lower levels of body mass index compared with counterparts of white European ancestry. Ectopic fat in skeletal muscle and liver are closely correlated with impaired whole-body insulin action. Ectopic fat may also be deposited in the pancreas and the heart and vascular system with detrimental effects on organ function.
[c] Various definitions of the metabolic syndrome have been proposed. The main features are abdominal adiposity, glucose intolerance, hypertriglyceridemia, low levels of HDL cholesterol, hypertension in variable combinations, and in association with insulin resistance and hyperinsulinemia.

In the context of age-related disease it has been suggested that "biological systems related to insulin metabolism are arguably the most critical regulators of longevity and corporeal ageing" [5]. However, while many metabolic pathways, including insulin-stimulated glucose disposal, become impaired with age, much uncertainty persists as to whether these are a cause or consequence of the aging process [6]. Moreover, the mechanisms accounting for the decline in metabolic function remain enigmatic.

The ability of insulin to stimulate glucose disposal varies at least six-fold in apparently healthy individuals [7]. Approximately one-third of the population that is most resistant to this, the best-documented action of insulin, is at greatly increased risk to develop a number of adverse clinical outcomes [7]. Disorders in which insulin resistance has been shown to have pathophysiological – and therapeutic – implications include obesity, states of glucose intolerance (impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)), type 2 diabetes, atherosclerotic cardiovascular disease, and heart failure [8–10]. The role of insulin resistance in the pathogenesis of type 2 diabetes is well established [11]. Non-pharmacological, that is, voluntary reductions in body weight coupled with increased levels of physical activity [12], and pharmacological interventions that improve insulin action are effective in preventing the progression of glucose intolerance to type 2 diabetes [13, 14].

15.2 Insulin physiology and metabolic regulation

Hepatocytes, skeletal myocytes, and white adipocytes are regarded as classic insulin-responsive tissues [15]. Insulin regulates glucose metabolism through direct actions [16] and in part by influencing inter-organ cross-talk pathways [17]. Insulin signaling within the brain influences energy balance and peripheral glucose and lipid metabolism [18]. Other non-classic target tissues for insulin include the heart [19], skeleton [20], brown adipocytes [21], and ovaries [22]. The physiological actions of insulin have expanded to embrace antioxidant, anti-inflammatory, and vascular effects [23, 24].

15.3 Insulin action: Relation to aging

Insulin resistance is implicated in common age-related diseases, including cognitive dysfunction [25] and frailty syndrome (Table 15.2) [26, 27]. The aging process is associated with impaired glucose homeostasis in part due to a decline in whole-body insulin action [28–30]. Insulin-mediated glucose uptake measured using the hyperinsulinemic euglycemic clamp technique declines

Table 15.2 Clinical disorders in which insulin resistance is implicated in pathogenesis[a] [4].

Glucose intolerance[b] and type 2 diabetes
Atherothrombotic cardiovascular disease
Essential hypertension
Polycystic ovary syndrome[c]
Non-alcoholic fatty liver disease[d]
Certain types of cancer
Sleep apnea
Cognitive decline
Frailty syndrome

[a] While not specific to aging, the prevalence of most of these disorders is highest among older age groups.
[b] Includes IFG and IGT.
[c] The clinical implications of polycystic ovary syndrome for postmenopausal women are unclear.
[d] Includes non-alcoholic steatohepatitis, which may progress to cirrhosis and hepatocellular carcinoma.
Cancer of breast, colorectal, liver, prostate and pancreas have been linked with insulin resistance.
Impaired function of major physiological systems, i.e. cardiac, hepatic and renal, is associated with insulin resistance.

progressively with aging [31]. Metabolic data in centenarians indicate that longevity is associated with preserved whole-body sensitivity to insulin (expressed as glucose disposal per fat-free mass) and glucose tolerance [32]. Studies of genetic polymorphisms associated with longevity have generated in excess of 100 candidate genes, some of which, for example the insulin and insulin-like growth factor (IGF-1) signaling pathways, are directly involved in the regulation of insulin sensitivity [33]. A unifying hypothesis has been proposed explaining the relationship between insulin resistance and aging that encompasses four main processes [31]:

- anthropometric changes, including increased fat mass with a parallel decline in fat-free mass
- environmental factors, for example unhealthy diet habits and reduced physical activity
- neurohormonal factors that antagonize the actions of insulin in key metabolically active tissues
- increased oxidative stress.

These pathways are considered in more detail later in the chapter, but it should be pointed out that the mechanisms through which insulin action is associated with longevity and freedom from age-related diseases remain unclear.

15.4 Implications of insulin resistance for cardiometabolic disease

While not a disease, the presence of the metabolic syndrome highlights traits that may confer an increased risk of adverse clinical outcomes [3, 34, 35]. Adults with the metabolic syndrome have evidence of endothelial dysfunction, an indicator of generalized vascular dysfunction, and a precursor of cardiovascular disease [36]. Among people with the metabolic syndrome there is an approximately two-fold increase in the risk of cardiovascular disease and five-fold or more for the development of type 2 diabetes mellitus [37]. Subdividing cardiovascular disease by vascular territory the metabolic syndrome is associated with a three- to four-fold increased risk of myocardial infarction, two- to four-fold increased risk of stroke, and a doubling of the risk of dying from such an event compared with individuals without the syndrome [38].

Diabetes and cardiovascular disease are closely interrelated. The common oil hypothesis posits that both may stem from a common etiology [39]. Insulin resistance is central both to the progression from normal glucose tolerance to type 2 diabetes and to the constellation of cardiovascular risk factors that comprise the metabolic syndrome [40]. The intimacy of the interrelation is such that myocardial infarction has been proposed as a diabetes risk equivalent. Cardiovascular disease is the leading cause of premature mortality in patients with type 2 diabetes [41]. Whether the metabolic syndrome is predictive of risk more than the sum of its component parts, each of which is a vascular risk factor in its own right, remains uncertain [42]. In this sense, the metabolic syndrome may be regarded as a multiplex risk factor for cardiovascular disease. It is possible that the total burden of risk over time imparted by the metabolic syndrome may exceed current estimates [43]. The metabolic syndrome appears to promote vascular aging by accelerating age-associated increases in arterial stiffness, a subclinical predictor of cardiovascular events [44]. An obesity-associated cardiomyopathy has been described

which is characterized by interstitial fibrosis and diastolic dysfunction [45]. The metabolic syndrome increases the probability of left ventricular hypertrophy, a powerful marker of cardiovascular events, even after adjustment for known etiological factors, including obesity and hypertension [46].

15.5 Clinical research methods for assessing insulin action

The importance of insulin resistance in human diabetes was demonstrated in a series of elegant clinical studies by Professor Sir Harold Himsworth in the 1930s [47]. Himsworth's experiments anticipated the modern classification of type 1 and 2 diabetes. As demonstrated by Himsworth, insulin resistance is not regarded as an intrinsic biochemical defect in type 1 diabetes, but insulin resistance may develop if overweight or obesity are superimposed on insulin deficiency [48]. In contrast, type 2 diabetes is usually associated with marked impairment of insulin action as an intrinsic biochemical feature of the disorder [49]. Insulin resistance is a key factor in the pathogenesis of type 2 diabetes [50].

Accurate quantification of insulin action for an individual is possible only within a clinical research setting. While obesity is usually associated with insulin resistance, body mass index (BMI) is a relatively unreliable indicator of insensitivity to insulin [51]. Visceral adiposity is associated with chronic inflammation, alterations in cytokine physiology, and an adverse profile of cardiometabolic risk factors [52].

15.6 Studies of insulin action in older people

Despite decades of investigation formidable barriers continue to impede elucidation of the role of insulin resistance in human disease. Insulin resistance is a highly heterogeneous state that remains imprecisely defined and is difficult to measure. The diverse array of physiological processes in which insulin is involved adds further layers of complexity. The focus of clinical studies of insulin resistance has mainly been directed to glucose metabolism. Decreased whole-body sensitivity to insulin in older people has been demonstrated using a range of investigative techniques [53]. Hyperinsulinemia after an oral glucose challenge is considered to be indirect evidence of reduced insulin sensitivity with a compensatory β-cell response [54]. A progressive decline in β-cell function has been documented with advancing age [55]. According to a widely accepted pathogenic model, hyperglycemia develops when islet β-cell function proves insufficient to fully compensate for insulin action in muscle and liver glucose intolerance. Ultimately type 2 diabetes develops as insulin secretion wanes over time [56]. Impaired β-cell responses to intestinally secreted incretin hormones, principally glucagon-like peptide-1, may contribute to age-related β-cell compensation [57].

Methods of varying sophistication have been developed to measure insulin action in clinical studies (Table 15.3). Pharmacological interruption of the feedback loop between the β-cell and insulin-sensitive tissues permits insulin-mediated glucose disposal to be quantified [28, 58]. The hyperinsulinemic euglycemic clamp is regarded as the reference method for quantifying insulin-mediated glucose disposal [59]. Under the conditions of sustained hyperinsulinemia attained during a hyperinsulinemic euglycemic clamp skeletal muscle is the primary tissue accounting for clearance of glucose from the circulation. In a study of non-diabetic, non-obese, physically active older people ($n = 17$, mean age 69 years) hyperinsulinemic euglycemic clamps spanning a range of plasma insulin concentrations were performed in order to examine whole-body

Table 15.3 Investigative techniques for the assessment of insulin action in humans [387].

Closed loop assessment of basal metabolism
Fasting insulin
Homeostasis model assessment (HOMA)
Closed-loop dynamic tests
A Endogenous insulin
Oral glucose tolerance test, for example Matsuda Index
Intravenous glucose tolerance test with minimal model assessment
B Exogenous insulin
Insulin tolerance test
Open-loop steady state tests
Insulin suppression test
Hyperinsulinemic euglycemic clamp

dose–response effects [28]. When compared with a control group of younger subjects ($n=27$, mean age 37 years) the dose–response curves in older subjects were shifted to the right, indicative of reduced insulin sensitivity. Lean body mass was approximately 10% lower in the older subjects. However, this was not considered to be responsible for the marked impairment of insulin sensitivity as a group. A significant inverse relationship between insulin-stimulated glucose disposal and age was evident in this study. Elevated blood glucose responses to an oral glucose challenge (with relative hyperinsulinemia) in the older subjects correlated with insulin resistance in peripheral tissues. The ability of insulin to suppress hepatic glucose production was also reduced in the older subjects [28]. According to Kahn's model of impaired insulin action [1], reduced maximal responsiveness to insulin, accompanied by evidence of normal binding of insulin to cellular receptors, was interpreted as evidence of a signaling defect distal to the binding of insulin to its cellular receptor. The European Group for the study of Insulin Resistance (EGIR) collected glucose clamp data from 20 European centers on 1146 men and women aged 18–85 years with normal glucose tolerance [58]. Whole-body insulin sensitivity, reported as the glucose disposal (M) value, declined with age at a rate of 0.9 mol/min/kg per decade of life. However, adjusting for BMI rendered the effect of age on insulin action no longer statistically significant; alternative estimates of insulin action yielded similar results. The investigators considered that the effect of age on insulin action could be explained by age-related changes in body composition and substrate competition. Evidence of a defect in the regulation of lipolysis was observed in men in this study [58]. This and other studies have also provided evidence for disordered lipid metabolism in age-associated insulin resistance. A study comparing healthy, lean, elderly subjects ($n=15$, mean age 70 years) with younger subjects ($n=13$, mean age 27 years) matched for lean body mass and fat mass found that the older participants were relatively insulin resistant compared with the younger control subjects [60]. This difference was attributed to reduced insulin-stimulated muscle glucose metabolism [23]. Lipolysis was assessed using isotopic tracers. Even although the percentage of body fat was similar between the groups, fasting non-esterified fatty acid (NEFA) concentrations were higher in the elderly subjects while concomitant insulin concentrations were similar between the groups; increased levels of fat accumulation were observed in muscle and liver tissue. This was accompanied by a ~40% reduction in skeletal muscle mitochondrial oxidative and phosphorylation activity measured using magnetic resonance spectroscopy [60]. In agreement with the aforementioned results of Fink *et al.* [28], basal hepatic glucose production, as determined using stable isotope tracer methodology, was similar for the young and elderly participants, and was suppressed completely in both groups [60].

15.7 Insulin resistance in clinical practice

The clinical relevance of the metabolic syndrome reflects the presence of several clinical risk factors for atherothrombotic vascular disease, that is, central adiposity, hyperglycemia, dyslipidemia (hypertriglyceridemia or low levels of high-density lipoprotein (HDL) cholesterol), and hypertension (Table 15.4) [61, 62]. Most patients (>80%) with type 2 diabetes have the metabolic

Table 15.4 Components of the metabolic syndrome [4].

Core defects
Resistance to insulin-stimulated glucose uptake
Obesity
Glucose intolerance
Hyperinsulinemia
Increased VLDL triglycerides
Decreased HDL cholesterol
Hypertension
Associated cardiometabolic abnormalities
Small dense LDL cholesterol particles
Hyperuricemia
Raised plasminogen activator inhibitor-1 concentrations
Elevated fibrinogen levels
Chronic systemic inflammation
Sympatho-adrenal activation
Endothelial dysfunction
Increased arterial stiffness

syndrome, but the converse is not necessarily true. The presence of other components of the metabolic syndrome at diagnosis of type 2 diabetes is associated with an increased risk of incident cardiovascular disease in the subsequent 5 years, with evidence of a dose–effect association, that is, risk increases with the number of components [63].

As discussed above, the clinical diagnosis of insulin resistance is dependent on the methodology used. The accepted gold standard for the assessment of whole-body insulin sensitivity in clinical research is the hyperinsulinemic euglycemic glucose clamp technique [59]. However, other approaches such as the modified insulin suppression test have been developed and utilized by Gerald Reaven [64]. Both of these techniques are technically challenging and labor intensive, being suitable only for use in specialized research units. Other less rigorous methods based on measures of fasting plasma glucose and insulin, for example homeostasis model assessment (HOMA)-IR [65] and the quantitative insulin sensitivity check index (QUICKI) [66], have been used for studies requiring larger numbers of subjects, where a simpler technique is necessary. Neither test is suitable for diagnosing insulin resistance at an individual patient level.

Clinical suspicion of the diagnosis usually starts with the recognition of obesity, especially of central abdominal distribution. Confirmation of the metabolic syndrome rests on the confirmation of the other key features [38]. A clinically useful laboratory biomarker for insulin resistance suitable for routine clinical use remains elusive [67]. While the finding of hyperinsulinemia in the presence of normoglycemia or hyperglycemia is characteristic of insulin resistance, the lack of standardization of insulin assays between laboratories renders cut-offs for insulin levels impractical [68]. Recent studies based on the detailed profiling of circulating metabolites – an approach known as metabolomics – have identified novel markers of insulin resistance, including branched chain amino acids and glycerol [67].

15.8 Metabolic syndrome: clinical definitions

Several attempts have been made to develop a definition of the metabolic syndrome that could be accepted worldwide. In 1998, the World Health Organization (WHO) proposed a set of diagnostic criteria [69]. This was followed by definitions from egir in 1999 [70] and by the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) in 2001 (Table 15.5) [71]. These definitions were in agreement that obesity, hyperglycemia, dyslipidemia, and hypertension were core components of the metabolic syndrome. However, they differed in certain details and specific criteria. Appropriate cut-off values for identifying individuals at risk from excess adiposity in Asian populations have been the subject of debate [72, 73]. In 2005, the American Heart Association and National Heart, Lung, and Blood Institute (AHA/NHLBI) published an amendment that included a reduced threshold for hyperglycemia and other minor modifications [74]. In 2005, the International Diabetes Federation (IDF) issued new criteria [38] which required the presence of central obesity plus any two of four components: elevated triglycerides, reduced HDL cholesterol, hypertension, and elevated plasma glucose (Table 15.6). The IDF waist circumference thresholds were lower than the ATP III criteria and included ethnicity-specific recommendations. The American Association of Clinical Endocrinologists (AACE) guidelines do not specify the number of factors required for the definition of the metabolic syndrome, leaving this to the judgment of the clinician [75]. Not included in these definitions, which were intended to be applied in clinical practice, are the pro-thrombotic state that is characteristic of

Table 15.5 NCEP ATP III clinical criteria for the metabolic syndrome [71].

Risk factors	Definition
Abdominal obesity, given as waist circumference	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dl (≥1.7 mmol/l)
HDL cholesterol	
Men	<40 mg/dl (<1.0 mmol/l)
Women	<50 mg/dl (<1.3 mmol/l)
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dl (≥6.1 mmol/l)

Table 15.6 IDF clinical criteria for the metabolic syndrome [38].

Central obesity (defined as waist circumference[a] with ethnicity specific values) plus any two of the following four factors:

- raised triglycerides
  ≥150 mg/dl (1.7 mmol/l)
  or specific treatment for this lipid abnormality
- reduced HDL cholesterol
  <40 mg/dl (1.03 mmol/l) in males
  <50 mg/dl (1.29 mmol/l) in females
  or specific treatment for this lipid abnormality
- raised blood pressure
  systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg
  or treatment of previously diagnosed hypertension
- raised fasting plasma glucose
  (FPG) ≥ 100 mg/dL (5.6 mmol/l)
  or previously diagnosed type 2 diabetes

If above 5.6 mmol/l or 100 mg/dl, an oral glucose tolerance test is strongly recommended.
* If BMI is >30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.

insulin resistance and which contributes to the elevated risk of cardiovascular events in affected individuals (see below) (Table 15.4) [76].

15.9 Utility of the metabolic syndrome in clinical practice

The metabolic syndrome has had something of a polarizing effect within the medical community. Some investigators have questioned the clinical utility of the syndrome [77]. The claim has been made that the primary clinical focus should remain on the individual metabolic risk factors and that the notion of a syndrome adds little to clinical management. The counter argument is that identification of risk factor clustering changes the clinical focus to underlying causes, which calls for greater emphasis on lifestyle therapies to reduce the long-term risks of diabetes and cardiovascular disease. This may be especially relevant in children and younger adults with the metabolic syndrome who face an increased lifetime risk of developing diabetes and its complications, including cardiovascular disease [78, 79]. Proponents argue that the metabolic syndrome was conceived as an indicator of increased relative risk of cardiovascular disease rather than for the estimation of absolute risk [80].

The modulating effects of aging, sex and co-morbidities add further layers of complexity to the risk of cardiovascular disease associated with the metabolic syndrome. Evaluation of coronary artery disease risk in subjects with the metabolic syndrome involves 10-year global risk estimation using the Framingham Risk Score or other algorithms for risk prediction. Consideration of screening for novel risk factors such as C-reactive protein (see below), as well as subclinical atherosclerosis (from carotid ultrasound, computed tomography or ankle-brachial index), may be used to further refine the estimation of future cardiovascular disease risk [81]. Heterogeneity of risk was demonstrated among 4293 US adults aged 20–79 years in the National Health and Nutrition Examination Survey 2003–2004 [82]. A range of global risk of coronary artery disease, from low to high according to the Framingham Risk Score, was identified [82]. In the absence of co-morbidities such as diabetes and cardiovascular disease, the metabolic syndrome does not appear to have predictive value superior to that of established risk scores. For example, in the Atherosclerosis Risk in Communities Study (ARIC) study of 12,089 black and white subjects aged 45–65 years the metabolic syndrome (as defined by ATP III) was present in approximately 23% of participants who did not have diabetes or prevalent cardiovascular disease at baseline [83]. Over an average follow-up of 11 years, 879 incident coronary artery disease and 216 ischemic stroke events occurred. Among the components of the metabolic syndrome, elevated blood pressure and low levels of HDL cholesterol exhibited the strongest associations with coronary artery disease. Men and women with the metabolic syndrome were approximately 1.5 and 2 times more likely to develop coronary artery disease than control subjects after adjustment for several potential confounding factors including age (sex interaction $p<0.03$). Similar associations were found between the metabolic syndrome and incident ischemic stroke. Comparison of receiver operating characteristic curves indicated that the metabolic syndrome did not materially improve coronary artery disease risk prediction beyond the level achieved by the Framingham Risk Score. An excess risk of coronary artery disease has also been documented among women with diabetes compared to their male counterparts [84]. The predictive value of the metabolic syndrome diagnosis for the

development of diabetes and cardiovascular events was assessed in two older population groups (aged 70–82 years and 60–79 years, respectively) [85]. BMI or waist circumference, triglycerides, and fasting glucose cut-off points were not associated with risk of cardiovascular disease. In contrast, all five components of the metabolic syndrome (ATP III criteria) were associated with risk of new-onset diabetes [85].

15.10 Prevalence of the metabolic syndrome

Estimates of the prevalence of the metabolic syndrome in different regions of the world depend on the defining criteria employed. Most reports have used the NCEP definitions of the syndrome [74]. In some studies, the NCEP definition has been adjusted for waist circumference differences in different population groups. One of the major unresolved issues for defining the syndrome is that of appropriate waist circumference. The primary difference between NCEP and IDF definitions is that waist circumference cut-off points for whites, blacks, and Hispanics is higher in NCEP than in IDF. For most countries according to recent estimates, between 20% and 30% of the adult population can be characterized as having the metabolic syndrome [43]. In North America, Latin America, Europe, and India at least one-quarter of adults have the syndrome [43]. Although there are inconsistencies in the literature regarding the influence of factors such as sex, ethnicity, and age [86], several population studies have reported an increase in the prevalence of the metabolic syndrome with age [87, 88].

15.11 Pathogenesis of the metabolic syndrome

The current obesity epidemic resulting from the modern western diet, which is relatively high in saturated fat, trans fatty acids, and refined sugars, is strongly implicated in the rising global prevalence of the metabolic syndrome [89]. The contribution of specific nutrients, for example sugar and high fructose corn syrup in beverages, is coming under increasing scrutiny [90]. The variable manifestation of the components of the metabolic syndrome reflects interactions of susceptibility genes [91]. It was recently reported that mutations in *DYRK1B*, which codes for an arginine-directed serine–threonine kinase, are associated with a clinical phenotype that is characterized by central obesity, hypertension, type 2 diabetes, and early-onset coronary artery disease [92]. In addition, adverse intra-uterine and early life experiences inducing epigenetic alterations [93, 94] together with exposure to numerous putative environmental factors, including pollutants that may disrupt endocrine signaling, have been implicated [95]. Sleep debt and obesity-associated obstructive sleep apnea contribute to insulin resistance [96, 97]. Both reduction in total sleep duration and alterations of sleep architecture are associated with impaired insulin action [98]. Circadian rhythms, energy balance, and metabolism also have a genetic component that has been demonstrated in mice [99]. A pathogenic role for altered gut microbiota in the development of obesity and the metabolic syndrome has also been hypothesized [100]. The metabolic syndrome is recognized as a side effect of several commonly used drugs, for example corticosteroids, antidepressants, and antipsychotics, that can produce weight gain thereby predisposing individuals to two of the features of the metabolic syndrome: obesity and glucose intolerance [101].

15.12 Overweight and obesity

Weight gain exposes individuals to two pivotal components of the metabolic syndrome, that is, obesity and insulin resistance. As mentioned above, there is a broad range of insulin sensitivity at any given level of body fat and a spectrum of obesity exists at any given level of insulin sensitivity. It is estimated that approximately 30% of the variability in insulin-mediated glucose uptake is accounted for by BMI, with physical activity levels and genetic influences contributing to the remainder of the variance [102, 103]. Anatomical distribution further modulates the metabolic consequences of excess adiposity. Aging is associated with progressive changes in total and regional fat distribution that have negative health consequences, that is, a preferential increase in abdominal fat, in particular visceral fat, combined with a decrease in lower body subcutaneous fat [104]. These age-related alterations in body composition, which may occur independently of changes in total adiposity, body weight or waist circumference, represent a phenotype closely associated with increased morbidity and mortality risk.

The disparate distribution [105] of fat between the sexes may help to explain why obesity had a more atherogenic effect in men than in women. The abdominal adipose distribution that is seen more frequently in men exerts a stronger adverse effect on cardiovascular risk than the gluteofemoral distribution usually observed in women [106, 107]. Abdominal adiposity is measured as waist circumference at the umbilicus or as the waist-to-hip ratio (WHR): waist circumference at the umbilicus divided by the hips' circumference at their widest point. A major continuing area of uncertainty is why some subjects do not develop metabolic complications of excess adiposity [108].

In addition to the anatomical regions of fat storage, ectopic fat deposition in liver, skeletal muscle, and myocardium is closely associated with dysfunction of these organs and reduced sensitivity to insulin when assessed at organ and whole-body level [109, 110]. However, the role of insulin resistance *per se* in the pathogenesis of cardiovascular disease has been difficult to differentiate from its close association with known risk factors such as hypertension and dyslipidemia [111, 112].

Adipose tissue has unique properties not shared by other organs, including an almost unlimited capacity to expand in a non-transformed state [113]. A sustained imbalance between dietary calories consumed and calories expended leads to storage of excess energy in the form of adipocyte intracellular triglyceride stores. The increase in fat mass manifests as both increased intracellular lipids and greater adipocyte size (hypertrophy) and increased numbers of adipocytes (hyperplasia) [114]. Adipose tissue is now recognized as an endocrine organ that secretes numerous factors that exert a range of metabolic effects.

15.12.1 Visceral adiposity

It has been shown in many studies that excess visceral fat is a risk factor for age-related diseases such as type 2 diabetes, hypertension, cardiovascular disease, and impaired cognitive functioning [115–119]. While both subcutaneous and visceral adipose tissue correlate with insulin resistance the relative contribution of visceral fat appears to be more marked [120]. It has been hypothesized that visceral obesity may be largely responsible for the clustering of risk factors that characterize the metabolic syndrome [121, 122]. Visceral fat is reportedly characterized by accelerated lipolytic activity [123]. The increased availability of NEFA adversely affects insulin action and glucose disposal in several tissues [124, 125]. The increase in circulating NEFA levels promotes triglyceride storage in muscle and liver, depressing insulin action and increasing hepatic output of very-low-density lipoproteins (VLDL) [126]. Conversely, reductions in visceral adiposity and NEFA levels following dietary-induced weight loss are associated with enhanced insulin sensitivity [127]. However, a causal relationship between visceral adiposity *per se* and insulin resistance has been questioned, with methodological limitations making the distinction between visceral and upper body obesity difficult to dissect [128]. There is mounting evidence that fatty infiltration of the liver in particular not only complicates obesity, but also perpetuates its metabolic consequences.

15.12.2 Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD), a disorder closely associated with hepatic and whole-body insulin resistance, the metabolic syndrome, and type 2 diabetes, has attained epidemic proportions [129]. NAFLD is gaining recognition as the liver manifestation of the metabolic syndrome. NAFLD has become the most common liver disease in Western countries, being found in 25-30% of the general population [130]. Among patients with type 2 diabetes the prevalence of NAFLD rises to >75% [131]. NAFLD embraces a wide range of metabolic hepatic damage characterized by steatosis and carries a risk of progression to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. NAFLD is common among the elderly, in whom it carries a more substantial burden of hepatic and extrahepatic manifestations and complications than in younger age groups [132]. As populations age the prevalence of NAFLD and NASH is predicted to increase further [133]. In addition to liver-related morbidity and mortality, clinical and epidemiological evidence is mounting that NAFLD is associated with an increased risk of atherothrombotic coronary heart disease, abnormalities of cardiac function and structure, for example left ventricular dysfunction, heart failure, aortic valve sclerosis, and atrial fibrillation [134]. Increased circulating NEFA concentrations reflect insulin resistance in adipocytes which promote inflammation and endoplasmic reticulum stress in the liver, aggravating and maintaining the insulin-resistant state in a vicious cycle [135]. Adipocyte-derived NEFA are the main source of hepatic triglycerides in NAFLD; hepatic de

novo lipogenesis and dietary fat also contribute [136]. It has been proposed that visceral adiposity may drive hepatic inflammation and fibrosis independently of the degree of liver steatosis [137].

The close associations between hepatic steatosis, cardiovascular disease, and diabetes have stimulated interest in interventions that target NAFLD with the aim of preventing diabetes [138, 139]. Dietary calorie restriction and exercise can be beneficial in improving features of the metabolic syndrome and surrogate markers of NAFLD [140]. Adherence to the Mediterranean diet may improve transaminase profiles but effects on liver histology have not been reported [141]. Bariatric surgery is also effective in decreasing the grade of steatosis, hepatic inflammation, and fibrosis in obese patients [142]. At present, no drugs are licensed for the treatment of NAFLD/NASH. Of drugs that have been tested as potential therapies thiazolidinediones, which activate the nuclear peroxisome proliferator-activated receptor (PPAR-γ) and improve insulin sensitivity, have been shown to improve insulin sensitivity, reducing hepatic transaminase levels and liver histology in some cases [143].

15.12.3 Role of adipocytokines

Systemic mediators of adipocyte dysfunction that impact health include adipocytokines, non-esterified fatty acids, and inflammatory markers. Fat-derived adipocytokines are soluble mediators involved in the interaction between adipose tissue, inflammation, and immunity [144]. Adipocytokines affect energy use and production, and are implicated in the pathophysiology of obesity and its systemic effects, including insulin resistance, hepatic steatosis, type 2 diabetes, and atherosclerosis [114].

Adipocyte hyperplasia and hypertrophy leads to increased production of leptin [145] and resistin [146]. It has been postulated that resistin, which is primarily produced by macrophages, is a potential link between inflammation and cardiometabolic disease. In contrast, circulating levels of adiponectin are reduced in obesity. Adiponectin is positively correlated with HDL levels and negatively with triglyceride levels, insulin resistance, and circulating inflammatory markers [147, 148]. Putative anti-atherogensic properties of adiponectin remain of uncertain clinical significance [149, 150]. The insulin-sensitizing actions of thiazolidinediones may in part be mediated via adiponectin [151].

15.12.4 Brown adipose tissue

In contrast to the largely deleterious metabolic effects of an expanded white adipose tissue mass the recent discovery of thermogenic brown adipose tissue (BAT) in a high proportion of adults has opened new lines of clinical investigation [152]. This has been confirmed using appropriate techniques, that is, cold exposure and positron emission tomographic imaging with ^{18}F-fluorodeoxyglucose [153]. In contrast to white adipose tissue, the principal function of which is energy storage, BAT is responsible for non-shivering thermogenesis by virtue of the presence of numerous mitochondria and cell-specific uncoupling protein-1. The latter increases the permeability of the inner mitochondrial membrane, decreasing the proton gradient generated in oxidative phosphorylation and uncoupling the respiratory chain. This favors substrate oxidation instead of adenosine triphosphate production. BAT is inversely related to total adiposity. Data from animal models and limited evidence in humans suggest that BAT is protective against obesity. Hyperinsulinemia also stimulates glucose uptake, albeit to a lesser extent than cold exposure. BAT tissue mass decreases with age, with older subjects having a less robust thermogenic response to cooling relative to young subjects [21]. Individuals with higher levels of BAT tend to have lower body weights and preserved health as they age [154]. Data from animal studies have stimulated speculation that BAT might not only regulate total body fat stores, but also modulate susceptibility to the metabolic, vascular, and degenerative diseases of aging [154]. The therapeutic potential of pharmacologically activating brown fat in humans is currently attracting much attention [155]. Evidence of plasticity has come from the demonstration that white adipocytes can be transformed by physical exercise into so-called "beige" cells which are intermediate between white and brown adipocytes [21]. A phosphoenolpyruvate carboxykinase-dependent hormone produced by skeletal muscle, called irisin, promotes the aforementioned browning of white adipocytes in response to physical exercise [156].

15.12.5 Low-grade inflammation

Obesity is characterized by a chronic low-grade inflammatory state with endothelial dysfunction. Chronic nutrient excess leads to expansion of visceral adipose tissue with relative hypoxia, adipocyte dysfunction, and accumulation of lymphocytes and

macrophages [157]. Monocyte-derived macrophages reside in adipose tissue and are at least in part the source of cytokine production locally and in the systemic circulation [158]. Obesity-associated pro-inflammatory cytokines that have been implicated in the pathogenesis of insulin resistance and atherosclerosis include tumor necrosis factor (TNF)-α [159] and interleukin (IL)-6. The role of the latter mediator has become less clear with the discovery that it is also a myokine that may mediate insulin-sensitizing effects of exercise [160]. The broader perspective of deranged cytokine profiles in visceral obesity and the metabolic syndrome includes C-reactive protein, IL-1β, IL-1 receptor antagonist, IL-10, and serum levels of soluble adhesion molecules (intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1), E-selectin, and P-selectin [161]).

15.12.6 Oxidative stress

Oxidative stress is implicated in the pathogenesis of obesity-associated insulin resistance, diabetes, and diabetes-related complications [162]. In recent years the pathological role of oxidative stress has been explored in the context of NAFLD [163] and Alzheimer's disease (see below) [164]. Originally proposed in the 1950s, the free radical theory of aging proposes that reactive oxygen species (ROS)-induced damage to cellular macromolecules is a primary driving force of aging and a major determinant of lifespan [165]. However, results from experimental models of antioxidant manipulation have cast doubt on the validity of the hypothesis [166]. It has become clear that there are multiple sources of intracellular ROS in mammals; these include NADPH oxidases, mitochondria, xanthine oxidase, monoamine oxidase, and nitric oxide synthase. This complexity may partly explain the mixed results observed in trials of antioxidants in diabetes and its complications [167].

15.12.7 Sex steroid hormones

The hormonal transitions that characterize the menopause [168] and decreasing levels of circulating androgens that may be observed in men as they age [169] also negatively impact on insulin sensitivity through combinations of direct and indirect mechanisms. The prevalence of the insulin resistance-associated metabolic syndrome increases during the peri-menopausal and early post-menopausal years; this increase appears to be driven at least in part by weight gain, particularly abdominal obesity [168]. In men, decreasing insulin sensitivity seems not to be entirely explained by the increased adiposity that accompanies low testosterone levels. A recent report from the European Male Ageing Study suggested that, after adjustment for confounders, insulin resistance was only evident in men with more severe degrees of late-onset hypogonadism [170]. Among older women with a putative postmenopausal polycystic ovary syndrome phenotype a dose–effect association was evident between the components of the syndrome and prevalent cardiovascular disease [171].

15.13 Role of insulin resistance

15.13.1 Glucose intolerance

As discussed earlier, insulin resistance is a cardinal defect in the pathogenesis of glucose intolerance and type 2 diabetes. The great majority of subjects with IFG [172], IGT [173] or type 2 diabetes [174] are insulin resistant as judged by established methods for evaluating insulin action. Insulin resistance in these states, even in the absence of diabetes, is not confined to glucose metabolism but may also be demonstrated in aspects of lipid metabolism [175, 176] and cardiovascular function [177]. Normal fasting plasma glucose is <5.6 mmol/l or a 2-hour plasma glucose in response to a 75-g oral glucose tolerance test (OGTT) <7.8 mmol/l. IGT is recognized as an intermediate level of postprandial glucose that carries essentially no risk for microvascular complications. IGT is diagnosed exclusively by OGTT; the 2-h plasma glucose is 7.8–11.0 mmol/l. According to National Health and Nutrition Examination Survey (NHANES) data the prevalence of IGT among adults in the USA aged >20 years is approximately 14% [178]. The prevalence of IGT rises progressively with age. In the European Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, the prevalence of IGT rose from 2.9% in 30- to 39-year-old men to 15.1% in 70- to 79-year-old men [179]. IGT is a relatively strong predictor of type 2 diabetes [12]. A predominant metabolic characteristic of IGT is insulin resistance in skeletal muscle, which is accompanied by hyperinsulinemia and defective insulin secretory dynamics [180]. In most Western countries, conversion rates for isolated IGT are approximately 4–6% per annum (14). In the Diabetes

Prevention Program (DPP), in which impaired fasting glucose also was also common, conversion to diabetes was approximately 10% per annum [12, 181].

IFG was introduced by the American Diabetes Association (ADA) in 1997 to classify fasting plasma glucose levels of 6.1–7.0 mmol/l [182]. By these criteria, the estimated US prevalence of IFG in adults >20 years of age was approximately 7% [183]. In 2003, the ADA changed its definition of IFG to a fasting level of 5.6–6.9 mmol/l [181]. The WHO defines IFG as a plasma glucose concentration ≥6.1 mmol/l and <7.0 mmol/l [69]. A combination of hepatic insulin resistance and defective insulin secretion in IFG results in excessive fasting hepatic glucose production, accounting for fasting hyperglycemia [181]. The natural history of both IFG and IGT is variable, with approximately 25% progressing to type 2 diabetes, 50% remaining in their intermediate glycemic state, and 25% reverting to normal glucose tolerance over 3–5 years [181]. Individuals who are older, overweight, and have other diabetes risk factors are more likely to progress. Subjects who satisfy the criteria for both IGT and IFG plus the metabolic syndrome are at greater risk for conversion to diabetes than are those with only IGT or IFG [181]. Longitudinal studies also indicate that both IFG and IGT are associated with a modest increase in the hazard ratio (approximately 1.1–1.4) for cardiovascular disease, with IGT being a slightly stronger risk predictor than IFG [181].

More recently, the use of hemoglobin (Hb)A_{1c} has been sanctioned, enabling subjects to be classified as normal <5.7 (<39 mmol/mol), pre-diabetes 5.7–6.4% (39–46 mmol/mol), and diabetes ≥6.5% (>48 mmol/mol) [184]. HbA_{1c} methods must be certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial reference assay.

15.13.2 Dyslipidemia

Insulin resistance is associated with a characteristic abnormal profile of blood lipids with enhanced atherogenic properties [185, 186]. Specifically this profile comprises:

- hypertriglyceridemia in the fasting and postprandial state
- triglyceride-enriched apolipoprotein (apo) B-containing lipoproteins
- small and dense LDL particles
- reduced HDL cholesterol levels.

The metabolic abnormality driving the dyslipidemia is increased hepatic assembly and secretion of VLDL particles, leading to increased plasma triglyceride (triacylglycerol) levels. VLDL can be divided into large, triglyceride-rich VLDL1 and small, dense VLDL2 [187]. Hypertriglyceridemia, in turn, results in a reduction in HDL levels with the generation of small, dense LDLs; these events are mediated by hepatic cholesteryl ester transfer protein (CETP) via increased catabolism of HDL apoA-I particles [185, 186].

Under physiological conditions, insulin readily inhibits adipocyte lipolysis while promoting lipogenesis [188, 189]. De novo synthesis of fatty acids and triacylglycerol occurs mostly in liver whereas adipose tissue is the primary site for triacylglycerol storage [189]. Insulin stimulates the activity of lipoprotein lipase, which hydrolyzes triglycerides in VLDL as well as chylomicrons liberating NEFA for uptake by adipose tissue [190]. By promoting the flow of intermediates through glycolysis within adipocytes insulin promotes formation of the α-glycerol phosphate, which is coupled with fatty acids to form triglyceride [191]. In insulin-resistant states, insulin is less effective in restraining lipolysis, leading to a rise in plasma concentrations of NEFA [175]. De novo lipogenesis is accelerated in the metabolic syndrome [192]. In addition, within the vasculature, reduced activity of lipoprotein lipase results in a slower catabolism of chylomicrons and VLDL, contributing to hypertriglyceridemia. Hypertriglyceridemia, both in the fasting and postprandial state, has been identified as a risk factor for coronary heart disease [193]. The triglyceride-enriched lipoproteins encountered in the metabolic syndrome are regarded as having enhanced atherogenic potential [186]. In addition to the direct atherogenic effect of triglyceride-rich lipoproteins, high levels of triglycerides and remnant particles appear to be inducers of a prothrombotic state [194]. This atherothrombotic diathesis is characterized by high concentrations of fibrinogen and PAI-1, and increased platelet aggregation [195].

The atherogenic profile in insulin resistance includes the presence of increased numbers of small, dense, and more atherogenic LDL particles that more easily cross the endothelial membrane and are more readily oxidized [196]. Triglyceride-rich VLDL particles result in slowly metabolized LDL particles with prolonged residence time in the circulation. These are subject to exchange processes that remove cholesteryl ester from

the particle core and replace it with triglyceride. Under these circumstances LDL is a potential substrate for hepatic lipase, generating smaller, denser particles [197]. The activity of hepatic lipase is increased in states of insulin resistance [198]. The higher concentrations of triglycerides in LDL particles is attributed to the activity of CETP, an enzyme that transfers triglycerides from VLDL to LDL [199]. The third altered lipid profile observed during the metabolic syndrome is the occurrence of lower HDL concentrations. The HDL particles are smaller and denser, and their size is inversely correlated with their triglyceride content – a phenomenon due to an increased catabolism of HDL [198, 200]. It has been proposed that the mixed dyslipidemia characteristic of the metabolic syndrome may contribute to insulin resistance and the well-recognized increased risk of type 2 diabetes [201].

Elevated plasma levels of LDL cholesterol are not considered to be a feature of insulin resistance and are not recognized as being a component of the metabolic syndrome [185, 186, 202]. When hypercholesterolemia coexists by chance with the metabolic syndrome, a not infrequent occurrence, the risk of cardiovascular disease is enhanced [82].

15.13.3 Arterial hypertension

Arterial – or systemic – hypertension co-segregates with many metabolic diseases, such as obesity, type 2 diabetes, atherosclerosis, and certain dyslipidemic states. An association between hyperinsulinemia and arterial hypertension was documented some 50 years ago [203]. Under experimental conditions in healthy subjects insulin has been shown to be a vasodilator, an effect mediated via generation of nitric oxide (NO) by endothelial cells [204, 205]. The physiological vasodilator effects of insulin are blunted in insulin-resistant states, leading to impaired vascular relaxation [206]. Defects in a common pathway between insulin-mediated NO production and the classic metabolic actions of insulin would result in both decreased vasodilatation and a reduced glucose skeletal muscle uptake [206, 207]. However, unravelling the myriad interactions between endothelial dysfunction, insulin-mediated vasodilation, decreased glucose disposal, and blood pressure has proved challenging [208–211]. Adding to the complexity of this hemodynamic-metabolic nexus is the vasocrine effect of locally produced adipocytokines from expanded perivascular adipose tissue (PVAT) in obese insulin-resistant individuals [212, 213]. The weight of the evidence appears to support the contention that insulin resistance precedes the development of hypertension. The enhanced cardiovascular risk associated with the metabolic syndrome in patients with high blood pressure may in part be mediated through progressive cardiovascular and renal damage, including left ventricular hypertrophy, subclinical atherosclerosis, impaired aortic elasticity, increased oxidative stress, and microalbuminuria [214–216].

The clinical associations between hypertension, insulin resistance, and other components of the metabolic syndrome have been demonstrated. A high proportion of otherwise healthy adults with hypertension have hyperinsulinemia relative to matched controls [217]. Non-obese and obese patients with newly diagnosed hypertension are insulin-resistant after correction for confounding variables [218]. Hypertensive subjects also tend to have glucose intolerance and hypertriglyceridemia [217, 218]. Conversely, whether non-obese or obese, subjects selected on the basis of higher plasma insulin responses to an oral glucose have higher systolic blood pressure together with features of the dyslipidemia characteristic of the metabolic syndrome [219]. These findings are independent of age, sex, generalized and abdominal obesity, cigarette smoking, and estimated physical activity [219]. Moreover, hyperinsulinemia, as a surrogate measure of insulin resistance, has been demonstrated to predict the development of IGT, type 2 diabetes, coronary heart disease, and hypertension [220, 221]. Thus the association between systemic hypertension and insulin resistance has been demonstrated by several groups of investigators using robust methods, including the hyperinsulinemic euglycemic clamp [222–224].

Other mechanisms have been proposed to explain the link between high blood pressure and insulin resistance. These include obesity-induced activation of the sympathetic nervous system with peripheral vasoconstriction and relative tachycardia (SNS) [225]. Obesity-associated hyperleptinemia also stimulates the SNS [226]. Activation of the renin-angiotensin-aldosterone system (RAAS) causes vasoconstriction and renal sodium retention [227]. Adipocytes possess all the components of the RAAS with the ability to produce angiotensin II, a powerful vasoconstrictor, and aldosterone [228]. Obstructive sleep apnea, which frequently

occurs in obese subjects, may also play a role via hypoxic activation of the chemoreceptors [229]. Furthermore, it has been suggested that the increased peripheral vascular resistance that often accompanies insulin resistance may be due in part to altered divalent cation metabolism of vascular smooth muscle cells (VSMC) [227]. Low levels of plasma natriuretic peptides in insulin-resistant subjects may also predispose to salt retention and increased activation of the SNS and RAAS [230].

15.14 Emerging role of insulin resistance and the metabolic syndrome in age-related disorders

15.14.1 Cognitive dysfunction

Cognitive impairment is highly prevalent among the older population. Insulin resistance and the metabolic syndrome are implicated in the development and progression of cognitive impairment with age as a modulating factor [231, 232]. Obesity, hypertension, dyslipidemia, glucose intolerance, type 2 diabetes, and insulin resistance are associated with an increased risk of cognitive impairment or dementia [231, 233, 234]. Diabetes is associated with a 1.5- to 2.5-fold greater risk of dementia among community-dwelling elderly people [235]. Diabetes is a significant risk factor for not only vascular dementia, but also Alzheimer's disease [235].

In recent decades it has become clear that the brain is an important target for insulin action. Insulin receptors are widely distributed throughout the central nervous system (CNS) [236]. Both neurons and glial cells may express insulin receptors [237]. Insulin action within the CNS modulates feeding behavior and body energy stores, influences peripheral glucose and lipid metabolism in liver and adipose tissue, and is involved in various aspects of memory and cognition [238]. Disruption of insulin action in the brain leads to impairment of neuronal function and synaptogenesis. Insulin also modulates phosphorylation of tau protein, an early component in the development of Alzheimer's disease. Thus, alterations in insulin action in the brain can contribute to the metabolic syndrome, and the development of mood disorders and neurodegenerative diseases. Insulin appears to play an important role in the cognitive decline that is associated with pathological brain aging [25]. Cross-sectional data demonstrate associations between measures of whole-body insulin resistance and impaired executive function times in older people without diabetes or dementia [239]. In a prospective observational study in 2632 older subjects those with the metabolic syndrome were more likely to have cognitive impairment. Progression of cognitive decline was associated with higher levels of the inflammatory markers IL-6 and CRP [240].

Whole-body insulin resistance reflects defects in insulin signaling in major metabolically active organs, that is, muscle, liver, and fat [241]. This is accompanied by reduced brain insulin levels and CNS insulin activity [242]. Impaired regional brain glucose uptake has been demonstrated in patients with Alzheimers's disease and mild cognitive impairment (MCI; see below) [243]. A proportion of plasma insulin is able to cross the blood–brain barrier via the insulin receptor on vascular endothelium [244]. However, some regions of the brain, such as the hypothalamus, may be more exposed to circulating insulin. Evidence has been gathering that insulin resistance within the CNS may be an independent risk factor for dementia [5]. It has been postulated that disturbances in cellular brain insulin signaling may contribute to the molecular, biochemical, and histopathological lesions in Alzheimer's disease [245]. The proximal cause of brain insulin resistance appears to be neuronal elevation in the serine phosphorylation of IRS-1, most likely due to amyloid-β-triggered microglial release of pro-inflammatory cytokines [246].

The state of pre-dementia known as MCI lies between normal aging and clinically evident dementia. MCI is estimated to affect approximately 10–20% of people aged 65 and over [247]. Nearly 50% of people with MCI will develop dementia within 3 years compared with approximately 3% of the general population. Risk factors for progression of MCI include depression and classic risk factors for cardiovascular disease [247]. A recent meta-analysis concluded that diabetes, prediabetes, the metabolic syndrome, and depression each increased the risk of conversion from MCI to Alzheimer's dementia [248]. A bi-directional relationship between type 2 diabetes and depression has been postulated. Diabetes and depression occur together approximately twice as frequently as would be predicted by chance alone [249]. Of note, insulin receptors are expressed in several brain regions associated with mood disorders [236]. Depression is also associated with the metabolic syndrome [250], again in a putative bidirectional

relationship [250]. There is also a well-recognized association between depression and cardiovascular disease [251]. Brain insulin resistance is also associated with Parkinson's disease, with a nearly two-fold increased risk in patients with diabetes in some studies [252].

Other metabolic factors that may influence cognitive function include insulin regulation of cerebral cholesterol metabolism and insulin-like growth factor (IGF)-1 signaling [236]. The brain is a very cholesterol-rich organ. Cholesterol within cell membranes contributes to synaptogenesis [253]. ApoE is the major apolipoprotein and the principal carrier of cholesterol in the brain. The ApoEε4 genetic variant is the most common risk factor for late-onset Alzheimer's disease [254]. In animal models of diabetes the synthesis of cholesterol within the brain is reduced [255]. Whether insulin resistance is a cause or consequence of Alzheimer's disease remains unclear. Insulin action plays a role in important aspects of the pathogenesis of Alzheimer's disease. Insulin signaling can counter pathological hallmarks of Alzheimer's disease, including aggregated amyloid-β fibrils and hyperphosphorylation of tau protein, causing amyloid plaques and neurofibrillary tangles [256]. In concert, these data indicate that defective insulin signaling is implicated in CNS disorders, including Alzheimer's disease. Insulin may also have a neuroprotective role in stroke [257].

No effective disease-modifying treatment currently exists for the common forms of age-related cognitive decline [258]. Evidence supporting improved glucose control, blood pressure, and lipid profiles in preventing cognitive decline is presently inconclusive [259]. The identification of impaired CNS insulin signaling has opened new therapeutic avenues focused on the metabolic component of the pathophysiology of Alzheimer's disease [242]. In animal models treatment with insulin and IGF-1 has been shown to decrease intracellular amyloid-β [236]. Proof-of-concept studies support intranasal insulin as a novel therapy for cognitive dysfunction. Intranasal insulin bypasses the blood–brain barrier, enabling high doses of insulin to be delivered directly into the CNS via the axons of olfactory cells and possibly other neuroanatomical routes. This approach avoids systemic hyperinsulinemia with the attendant risk of hypoglycemia [260]. In a 4-month study intranasal insulin stabilized or improved aspects of cognitive function in patients with Alzheimer's disease dementia or MCI [261]. These effects were accompanied by altered progression of impaired regional cerebral glucose metabolism [261]. The cognitive response to intranasal insulin appears to be dependent on factors including sex, insulin dose, and ApoEε4 status, underscoring the complexity of insulin action in the brain [262, 263]. Longer-term trials are in progress.

Repositioning other classes of glucose-lowering drugs for the prevention of Alzheimer's disease has been proposed in recognition of the need for effective disease-retarding therapy [264, 265]. The available clinical evidence for thiazolidinediones and metformin in countering cognitive decline is inconsistent [264]. Newer classes of diabetes appear more promising in terms of potential utility for countering metabolic contributions to cognitive decline. In addition to systemic effects on insulin and glucose metabolism it has been hypothesized that glucagon-like peptide (GLP)-1 receptor agonists may be able to circumvent impaired CNS insulin signaling and re-establish signal transduction through the insulin-like substrate-1 (IRS-1) → Akt pathway [264]. GLP-1 receptor agonists and dipetidyl peptidase (DPP)-4 inhibitors have neuroprotective properties [264, 266]. In the context of MCI, preclinical data suggest that GLP-1 receptor agonists may result in increased hippocampal growth and improve cognitive performance [267] while DPP-4 inhibitors may protect against cognitive impairment in insulin-resistant animal models [268]. The results of clinical trials with GLP-1 receptor agonists and other novel glucose-lowering agents in patients with cognitive dysfunction are awaited [264, 265].

15.14.2 Frailty syndrome

The term "frailty" denotes a geriatric syndrome characterized by reduced homeostatic reserves that increases the risk of negative health-related events including falls, hospitalization, progressive disability, institutionalization, and mortality [269, 270]. While impairment of aspects of physical functioning is the main hallmark of frailty psychological, cognitive factors may contribute and interact with one another [271, 272]. In a 4.4-year longitudinal study of 1567 participants aged 65–96 years pre-frailty, defined as the presence of one or two modified Fried criteria (unintentional weight loss, low physical activity level, weakness, exhaustion, and slow gait speed) independently predicted incident cardiovascular disease [273]. Both conditions are characterized by generalized inflammation and cause-and-effect relationships remain uncertain.

Aging is associated with a decrease in lean body mass, especially muscle tissue [274] with reductions in the size and number of muscle fibers [275]. Sarcopenia – defined as age-related loss of muscle mass with consequent loss of strength [276] – is a core physical feature of frailty [277]. Sarcopenia is distinct from muscle wasting, which more broadly refers to involuntary loss of body mass that includes both muscle mass and fat [278]. In older persons, poor muscle strength and poor physical performance often coexist and have their origins in pathological processes that are initiated decades earlier. Thus, in longitudinal studies handgrip muscle strength in midlife predicts functional capacity in old age [279]. The prevalence of sarcopenia rises with age, with approximately 10–50% of people ≥80 years being affected [280]. The etiology of sarcopenia is complex, with reduced anabolic hormone production, decreased sensitivity to insulin, dysregulation of cytokine secretion, altered responses to inflammatory events, inadequate nutritional intake, and sedentary lifestyle all being implicated [281, 282]. Insulin resistance is associated with several features of frailty such as skeletal muscle loss and weakness, lower extremity mobility disability, and body composition changes [27]. Moreover, sarcopenic obesity in elderly subjects adds the risk of the metabolic syndrome due to loss of muscle mass [282]. Several computed tomography, magnetic resonance imaging, and ultrasonography studies have shown that in sarcopenia, the loss of muscle tissue is accompanied by infiltration with lipid [283].

Insulin has a pivotal role in muscle contraction by stimulating glucose uptake and promoting intracellular glucose metabolism. Thus, it is plausible that age-related insulin resistance may be a determinant of reduced muscle functioning manifested clinically by reduced muscle strength. However, given its prime role in insulin-mediated glucose disposal sarcopenia would be predicted to predispose to the development of insulin resistance and type 2 diabetes [284]. Another important role played by insulin is its ability to repress whole-body proteolysis, thereby shifting total body metabolism towards an anabolic state [285]. It is plausible that a reduction in insulin action within skeletal myocytes may exacerbate impaired cellular anabolism, thereby creating a vicious cycle. Insulin resistance may accelerate cellular autophagy, including lysosomal degradation of proteins, via reduced mammalian target of rapamycin (mTor) kinase signaling [286]. A role of defective mitochondrial function in sarcopenia-associated insulin resistance has been postulated but the data are inconsistent and of uncertain clinical relevance [287, 288]. Countering age-related insulin resistance in muscle protein synthesis may require supraphysiological insulin concentrations [289]. In the context of diabetes, cross-sectional and longitudinal studies have shown that accelerated loss of muscle mass is greater with longer diabetes duration and higher HbA1c levels and may be attenuated by insulin-sensitizing drugs [290, 291]. Regular exercise is the only strategy found to consistently prevent frailty and improve sarcopenia and physical function in older people. Resistance exercise training is more effective in increasing muscle mass and strength, whereas endurance training is superior for maintaining and improving maximum aerobic power [292].

As mentioned above, skeletal muscle produces a range of cytokines and peptides – termed myokines – that communicate with other tissues [293]. Since myokines are dependent on muscular contraction, it has been hypothesized that the association between physical inactivity and some chronic diseases may be mediated via altered myokine responses [293]. Myostatin, a recently discovered myokine, is a potent negative inhibitor of muscle growth [294]. Pharmacological agents that block myostatin have entered clinical trials. While maximum muscle strength and power decrease with aging even in highly trained master athletes there is evidence that strength training may counter sarcopenia even in the very elderly [295]. Physical exercise induces IGF-1, its receptors and phosphatidylinositol 3-kinase, mitogen-activated protein (MAP) kinase, and calcineurin signaling pathways [296]. Nutritional factors that have been implicated in the pathogenesis of sarcopenia include fatty acids, antioxidants, amino acids, and amino acid derivatives [297, 298]. Dietary supplements have being explored as potential therapies to counter sarcopenia, as has correction of age-related hormone deficiencies, including sex steroid hormones, growth hormone, ghrelin, and vitamin D [299].

15.15 Controversies in prevention and therapy of the metabolic syndrome

The cardiometabolic risk factors that comprise the metabolic syndrome include glucose intolerance, an atherogenic lipid profile, hypertension, a prothrombotic

diathesis, and a pro-inflammatory state. Obesity-associated insulin resistance has been proposed as a key player in the metabolic syndrome. The more overweight an individual, the more likely he or she is to be insulin resistant and to be at increased risk of developing all the abnormalities associated with impaired insulin action [9]. Thus maintenance of optimal body weight has a central role in preventing the metabolic syndrome and reversing the key features of the syndrome. Lifestyle and, where indicated, pharmacological interventions may favorably alter the metabolic profile and modify the risk of progression to diabetes [300]. However, some aspects of the cost-effectiveness of these interventions remain unclear [301].

Consensus panels recommend multidisciplinary therapeutic lifestyle counseling as first-line treatment for the metabolic syndrome [71, 101]. The recommendations, which have been echoed in other reports, include increased levels of physical activity (approximately 30 minutes of brisk walking daily) for sedentary individuals, a reduced-energy (approximately 500–1000 calories/day reduction) low-fat, low-*trans*-fat, high-complex-carbohydrate diet, and incorporation of physical activity, stress management, and group support for effective long-term weight management. The evidence base and recommendations for prevention of cardiovascular disease and obesity have since been updated by organizations including the American College of Cardiology, the American Heart Association, and the ADA [302–304]. In a recent meta-analysis of randomized controlled trials lifestyle modification was effective in causing resolution of the metabolic syndrome and reducing the severity of related abnormalities, including fasting blood glucose, waist circumference, blood pressure, and triglycerides [305].

The only way to prevent or delay the development of microvascular complications in patients with impaired glucose regulation is to prevent or delay the development of diabetes. Currently, there is no effective way to prevent the decline in β-cell function in individuals destined to develop type 2 diabetes, therefore priority must be given to reducing insulin resistance. This is most appropriately achieved through lifestyle intervention, that is, weight reduction and increased levels of physical activity. The DPP demonstrated the efficacy of this approach in high-risk obese subjects with pre-diabetes, albeit within the setting of a well-resourced clinical trial [12]. Similar results were reported in the Finnish Diabetes Prevention Study (DPS) [306]. Importantly, both of these studies demonstrated sustained benefits beyond the randomized intervention period [307, 308]. The Da Qing study in China also demonstrated that group-based lifestyle interventions over 6 years may prevent or delay diabetes in subjects with IGT for up to 14 years after active intervention [309].

Approximately half the participants in the DPP had the metabolic syndrome at baseline. Both lifestyle intervention and metformin therapy reduced the development of the syndrome in the remaining participants [310]. In the DPP, metformin therapy delayed conversion of pre-diabetes to diabetes in approximately 40% of participants [12]. This has led to a recommendation by some diabetologists for the use of metformin in persons with IFG plus IGT and other metabolic syndrome risk factors. The Glucose Lowering in Non-diabetic hyperglycemia Trial (GLINT) is a multi-center, randomized, double-blind, parallel group, pragmatic, primary prevention trial comparing the effect of slow-release metformin with placebo on a composite macrovascular outcome in people with pre-diabetes and high risk of cardiovascular disease (http://www.dtu.ox.ac.uk/glint). No drug therapy is currently licensed for the prevention of type 2 diabetes. Nonetheless, the UK National Institute for Health and Care Excellence (NICE) has advocated consideration of metformin in adults at high risk whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes despite participation in an intensive lifestyle-change program [311]. The ADA also recommends consideration of metformin as an adjunct to lifestyle measures for selected patients in the prevention of type 2 diabetes [304]. Specifically, the ADA states that metformin therapy for prevention of type 2 diabetes may be considered in groups including individuals with IGT, IFG, and HbA1c 5.7–6.4%, especially for those with BMI >35 kg/m^2, aged <60 years and women with a history of gestational diabetes mellitus. In the DPP, metformin was only effective in participants <60 years of age [12].

In addition to metformin, several other glucose-lowering, anti-obesity or cardiovascular drugs have shown to reduce the incidence of type 2 diabetes in people with impaired glucose regulation [312–318]. Of these, troglitazone was withdrawn from the market because of serious hepatoxicity [319]. In 2010, rosiglitazone was withdrawn in Europe and its use was restricted in the USA in response to concerns about cardiotoxicity [320].

In the light of the current evidence base, individuals with pre-diabetes or the metabolic syndrome should be encouraged to engage in a lifestyle intervention program. Professional assistance may be useful, although resources vary widely between healthcare systems. The effects of calorie restriction on body weight are enhanced by exercise. Current evidence suggests that resistance training may promote a negative energy balance and may change body fat distribution [321]. In the context of the metabolic syndrome increased muscle mass with resistance training may mediate better metabolic control [321]. Patient motivation leading to improved lifestyle adherence is a key factor determining the success of lifestyle modification on the components of the metabolic syndrome. While motivation can be enhanced via frequent encounters with the healthcare system, use of technologies such as mobile and internet-based communication may support the effectiveness of lifestyle change in the metabolic syndrome [322].

Judicious use of drug interventions, either directly to improve insulin sensitivity or indirectly to improve the metabolic changes associated with insulin resistance, may also be considered. However, no single drug offers a fundamental intervention for the metabolic syndrome. Novel approaches, for example targeting microRNA-mediated pathways and mitochondrial dysfunction, are being explored [323, 324]. The potential for drugs targeting one facet of the metabolic syndrome to aggravate others should be borne in mind. Four classes of drugs that are commonly used with the intention of reducing cardiovascular risk – statins, niacin, thiazide diuretics, and certain β-blockers – have been shown to increase the risk of new-onset diabetes in meta-analyses or large-scale clinical trials [325]. The risk of drug-induced de novo diabetes is heightened by the presence of features of the metabolic syndrome [325].

15.15.1 Medical nutrition therapy

The beneficial cardiovascular and metabolic effects of a Mediterranean diet have become evident in recent years [326, 327]. The diet, which consists of fish, monounsaturated fats from olive oil, fruits, vegetables, whole grains, legumes/nuts, and moderate alcohol consumption, improves cardiovascular disease risk factors, including WHR, lipids, and markers of inflammation, as well as primary cardiovascular disease outcomes such as death and events in both observational and randomized controlled trials [327]. In the PREDIMED trial of men and women aged 55–80 at high risk of cardiovascular disease 64% of participants had the metabolic syndrome at baseline. Participants were randomized to follow one of three diets: a low-fat diet, a Mediterranean diet supplemented with nuts or a Mediterranean diet supplemented with extra-virgin olive oil. The interventions did not include increased physical activity nor was weight loss a goal. Over an average follow-up of almost 5 years participants who followed the Mediterranean diet supplemented with nuts and the Mediterranean diet supplemented with extra-virgin olive oil saw a reduction in blood glucose levels and abdominal obesity. Furthermore, 28% of participants who followed the Mediterranean diets no longer met the criteria for the metabolic syndrome by the end of the study [328]. No differences were observed between the diets in weight loss or energy expenditure from physical activity. The incidence of new cases of the metabolic syndrome in participants who did not have it at baseline was similar in all three groups.

The benefits of lifestyle interventions on cardiovascular disease are less clear. In the Da Qing study, no significant difference was observed between the intervention and control groups in the rate of first cardiovascular events, cardiovascular mortality or all-cause mortality [309]. However, the study had limited statistical power to detect differences for these outcomes. The LookAhead trial was a randomized controlled trial of intensive lifestyle intervention to support and education in overweight and obese type 2 diabetes patients on the development of cardiovascular disease over time. The trial was terminated after a median follow-up of 9.6 years [329]. While weight loss was greater with intensive therapy and glycemic control, lipid profiles and fitness were all improved, and there was no reduction in cardiovascular events [330].

Advances in understanding of gene–nutrient interactions in the context of the metabolic syndrome may offer a more personalized approach to medical nutrition therapy in the future [331].

15.15.2 Anti-obesity drugs

Voluntary weight loss has beneficial effects on multiple aspects of the metabolic syndrome, including reducing or delaying the risk of progression from states of impaired glucose regulation to type 2 diabetes [303]. In 2012 NICE recommended that orlistat be considered in

people with a BMI of 28.0 kg/m^2 or more as part of an overall plan for managing obesity [311]. In 2013, the American Association of Clinical Endocrinologists incorporated anti-obesity drugs into a comprehensive management algorithm for pre-diabetes and diabetes [332]. New anti-obesity drugs approved in the USA and/or Europe including lorcaserin, phentermine/extended-release topiramate, buproprion/naltrexone, and liraglutide 3.0 mg, have expanded the pharmacological options for weight reduction with attendant improvements in cardiometabolic profiles [333–335]. Accordingly, a greater role for anti-obesity drugs in the prevention and treatment of obesity-associated type 2 diabetes may be envisioned [336].

15.15.3 Bariatric surgery

Trials of bariatric surgery in patients with morbid obesity and the metabolic syndrome showed beneficial results, including decreased insulin resistance and lower levels of inflammatory cytokines [337]. Bariatric surgery can significantly reduce body weight and result in resolution of many cardiovascular risk factors, including type 2 diabetes, hypertension, and hyperlipidemia, with improved long-term survival [338]. The risks and benefits of bariatric surgery in older patients merit further study [339].

15.15.4 Blood pressure control

Less marked elevations of blood pressure can often be controlled by lifestyle changes, including a reduced sodium intake and weight loss. When pharmacotherapy is necessary, knowledge of the effects of various classes of antihypertensive drugs on glucose metabolism and insulin sensitivity should inform the decision-making process [340]. The metabolic effects of antihypertensive drugs appear to mediate, at least in part, the attendant risk of new-onset diabetes associated with their use [341, 342]. Angiotensin receptor blockers and angiotensin converting enzyme inhibitors have been associated with beneficial effects on glucose homeostasis. Telmisartan reportedly has agonist effects at the peroxisome proliferator-activated receptor (PPAR)-γ receptor [343]. Calcium channel blockers are generally regarded as having neutral effects on glucose metabolism. However, some members of this class, such as azelnidipine [344] and manidipine [345], have been shown to have advantageous effects on insulin action and glucose homeostasis. Moxonidine is a centrally acting imidazoline type-1 receptor agonist with insulin-sensitizing actions and beneficial effects on blood lipid profiles [346, 347]. The α-1 adrenergic blocker doxazosin also improves insulin sensitivity [348]. However, doxazosin was associated with a higher risk of heart failure compared to the diuretic [349] chlorthalidone in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diuretics and β-adrenergic blockers tend to have disadvantageous effects on glucose metabolism and insulin sensitivity [340]. Non-selective β-adrenergic blockers are associated with weight gain [350]. However, vasodilating β-blockers such as carvedilol and nebivolol are credited with less marked or neutral metabolic effects [351].

The 2014 report of the JNC-8 included less stringent recommendations for drug therapy (140/90 mmHg for most populations, 150/90 mm Hg for patients aged 60 or older) compared to JNC-7 [352], which was not universally recommended by the committee members [353].

15.15.5 Lipid-modifying drugs

15.15.5.1 Statin therapy and cholesterol-lowering guidelines

A cornerstone of reducing global risk of cardiovascular disease is lowering LDL cholesterol using statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) at all indicated ranges, as there are several formulations available with different doses and potencies. Statins affect the lipid profile favorably and provide possible pleiotropic benefits [354]. The choice of drug and dose should be individualized to the patient and titrated to achieve guideline-recommended goals [355]. Statins have reduce LDL cholesterol levels by approximately 20–50% and triglycerides by 10–40%, and may increase HDL cholesterol levels by 5–10%.

The 2001 ATP III guideline proposed thresholds for therapeutic lifestyle changes, that is, weight management and increased physical activity [71]. Initiation of lipid-modifying drug therapy and targets for LDL cholesterol were also recommended according to individual calculated risk. The guideline proposed that lipid and non-lipid risk factors, that is, hypertension, using aspirin to counter a pro-thrombotic state, and treating elevated triglycerides and/or low HDL cholesterol levels, should be treated if they persisted despite lifestyle therapies. This approach was modified in the light of additional clinical trial evidence and became established clinical practice [356]. In 2013 new

guidance was issued by the American Heart Association and the American College of Cardiology to replace the widely used ATP III guideline from the National Heart, Lung, and Blood Institutes, which had last been updated in 2004. The 2013 guideline introduced a new 10-year risk calculator that included age, sex, race, total cholesterol, HDL cholesterol, and systolic blood pressure [357]. Furthermore, the new guideline emphasized the use of statins over non-statin therapies, based on evidence from randomized controlled trials [357]. The guidelines lowered the thresholds for the 10-year risk of non-fatal and fatal coronary artery disease and stroke to 7.5% or higher, and recommend a tiered system of statin therapy to reduce risk. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of one or more of family history of atherosclerotic cardiovascular disease, high-sensitivity C-reactive protein, coronary artery calcium score, or ankle-brachial index may be considered to inform treatment decision making. Four groups were identified, for whom an extensive body of clinical trial evidence has demonstrated a reduction in atherosclerotic cardiovascular disease events using statin therapy. The intensity of the statin therapy recommended reflects the absolute risk of cardiovascular events based on group averages and applied to individual patients in practice. Treatment targets for lipids were not included since these are not supported by the clinical trial evidence. Accordingly, LDL cholesterol levels and percentage reduction are to be used only to assess response to therapy and adherence. High-intensity statin therapy generally results in an average LDL cholesterol reduction of ≥50% from the untreated baseline. Moderate-intensity statin therapy generally results in an average LDL cholesterol reduction of 30% to <50% from the untreated baseline. The ADA endorsed the guidelines, albeit with some modifications [358]. The 2013 cholesterol management guidelines, which have been described as a paradigm shift for most clinicians and patients, have generated controversy on several fronts since their publication, ranging from the abandonment of lipid targets to the accuracy of the new risk calculator and the exclusive focus on statins [359, 360]. In contrast to the ATP III guidelines the 2013 guidance does not explicitly consider the metabolic syndrome.

In the context of what is still an ongoing debate it is pertinent to consider current developments in pharmacological lipid-lowering strategies for high-risk individuals. The 2013 cholesterol guidelines of the American College of Cardiology and the American Heart Association recommend that non-statins can be used in higher-risk patients in whom statin therapy does not lower LDL cholesterol levels sufficiently or in patients with unacceptable side effects from statin therapy, with a strong preference for use of non-statins that have been determined to be safe and effective in randomized controlled trials. The results of recent clinical trials seem likely to lead to amendments to the cholesterol guidelines. Trials of a new class of potent LDL-lowering drugs – the pro-protein convertase subtilisin/kexin-9 (PCSK9) inhibitors [361, 362] – have now been reported. These drugs have the capacity to exceed the LDL-lowering effect of statins. As compared with placebo or standard therapy, evolocumab and alirocumab reduce LDL cholesterol levels by an average of approximately 60% [363]. As with statins, levels of apolipoprotein B and triglycerides were lowered by treatment, and levels of apolipoprotein A1 and HDL cholesterol are increased. Thus, PCSK9 inhibitors appear to address the lipid subfractions relevant to the metabolic syndrome. Unlike statins, significant reductions in another metabolic syndrome risk marker, lipoprotein (a) [364], have also been observed. Both drugs have clinical trial data in high-risk patients showing approximately 50% reductions in composite cardiovascular events at 12–18 months [363]. Reports of neurocognitive side effects with PCSK9 inhibitors require further evaluation. Alirocumab and evolocumab were approved by the FDA in 2015.

The recently published IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that in high-risk patients with recent acute coronary syndromes, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing cardiovascular events. This is the first study powered for clinical outcomes to show a benefit with a non-statin agent (ezetimibe, a cholesterol absorption inhibitor) when added to a statin, thereby providing support for the LDL cholesterol hypothesis [365, 366]. On subgroup analysis, patients with diabetes had greater benefit of ezetimibe/simvastatin (hazard ratio 0.86, p for interaction = 0.023).

Randomized controlled trials and meta-analyses suggest an increase in the risk of new-onset diabetes with statins, particularly with higher intensity regimens in people with two or more components of the metabolic syndrome [367]. This unanticipated adverse metabolic

effect of statins has generated debate about the risks and benefits of statin therapy, especially at higher doses. However, the consensus opinion is that, for high-risk patients, the proven clinical benefits of statins outweigh the risk of diabetes [368]. The magnitude of the risk of diabetes varies between statins.

Data continue to accrue, with a recent study reporting a 46% increase in the risk of developing diabetes, the highest risk observed to date [369]. This excess risk was evident after adjustment for confounding factors such as age, BMI, waist circumference, physical activity, and family history of diabetes. The investigators studied 8749 non-diabetic men aged 45–73 years in a 6-year follow-up of the population-based Metabolic Syndrome in Men (METSIM) study, based in Kuopio, Finland. New diabetes was diagnosed in 625 subjects by an oral glucose tolerance test (OGTT), an HbA1c level of 6.5% or higher, or start of glucose-lowering medication. A dose-dependent risk of diabetes was observed for simvastatin and atorvastatin. Insulin sensitivity, modelled from OGGT glucose and insulin responses, was decreased by 24% while insulin secretion was reduced 12% in individuals on statin treatment [369]. Statin therapy was associated with raised post-challenge glucose levels more than fasting glucose concentrations. While the precise mechanisms responsible for statin-induced diabetes remain uncertain [370], evidence of an on-target effect has been found in an analysis of genetic and clinical trial data [371]. Recent data suggest that familial hypercholesterolemia may be associated with a decreased risk of type 2 diabetes [372]. This observation, if confirmed in longitudinal studies, raises the possibility of a causal relationship between LDL receptor-mediated transmembrane cholesterol transport and type 2 diabetes. One member of the statin class (pitavastatin) is reportedly associated with neutral or favorable effects on glucose control in patients with and without type 2 diabetes or the metabolic syndrome [373]. Pitavastatin also raises HLD cholesterol levels [374]. However, no clinical trial data with cardiovascular endpoints are available for this drug.

15.15.5.2 Hypertriglyceridemia

Intensive lifestyle therapy is the main initial treatment of hypertriglyceridemia. If required, fibric acid derivatives (bezafibrate and fenofibrate for monotherapy and combination with statin; gemfibrozil only for monotherapy) are the preferred drugs [375]. Fibrates are ligands for the PPAR-α nuclear receptor [376]. Fibrates appear to provide particular benefit to patients who exhibit the high triglyceride/low-HDL cholesterol profile of the metabolic syndrome [377].

15.15.5.3 HDL cholesterol

The management of reduced HDL cholesterol *per se* remains controversial and starts with diet and exercise; currently available drug options to raise HDL cholesterol levels have limited efficacy [378]. Uncertainty about whether raising HDL cholesterol will translate into reduced cardiovascular events awaits the results of ongoing trials of CETP inhibitors [361, 379]. Other classes of drugs with effects on HDL cholesterol are also in development [380]. The failure in recent clinical trials aimed at raising HDL cholesterol to yield the expected improvement in clinical outcomes highlights limitations in the understanding of HDL particle function and metabolism [381]. Recent data suggest that low HDL cholesterol levels may contribute to the pathogenesis of type 2 diabetes [382].

15.15.6 Anti-platelet therapy

Aspirin therapy may be helpful in the primary prevention of cardiovascular complications [383] in patients with at least an intermediate risk of sustaining a cardiovascular event.

15.15.7 Complementary and alternative therapies

There is limited evidence in the literature supporting the use of complementary and alternative medications for the metabolic syndrome. Ginseng, berberine, and bitter gourd have demonstrated favorable metabolic effects, but large-scale clinical trials of safety and efficacy are needed [384]. Other complementary and alternative treatments may have a potential role in the management of the metabolic syndrome; further study seems warranted [385]. Postulated therapeutic roles for resveratrol and sirtuin activators for insulin resistance and obesity-associated diseases remain unsubstantiated [386].

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CHAPTER 16

Diabetes and functional limitation: The emergence of frailty and disability

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KEY MESSAGES

- A key priority in the management of older people with disease is to avoid or delay the appearance of functional decline, clinically manifested as frailty and disability.
- Functional impairment and physical disability directly attributable to diabetes have not been studied in depth, although it has been known for several years that these are direct threats to personal independence and quality of life.
- Frail older patients with diabetes have a higher mortality than their non-frail counterparts.
- Frailty is the most important predictor of death in older adults with diabetes, emphasizing the importance of functional assessment.
- Diabetes is a model of disability but the traditional macro- and microvascular complications account for less than 40% of the incident disability.
- Avoiding functional decline and impairment in these patients demands an active management approach to detect those at risk and those in the first stages of the disabling process, where there is still an opportunity (i.e., enough functional reserve) for intervention.

16.1 Introduction

After the discovery of insulin and its subsequent wide use, the profile of diabetes as a disease changed. In the second third of the last century the typical patient was a middle-age man/woman who was overweight or obese, with cardiovascular disease. Now, with increasing life expectancy, changes in lifestyle and a better control of chronic diseases, the more common patient with diabetes is an older adult with a high risk of developing functional (physical and cognitive) impairment. Moreover, as we will show in this chapter, functional status is a main predictor factor for several adverse outcomes in older adults with diabetes.

As a natural consequence of the changes in the profile of the patient, a change in therapeutic priorities has also occurred. While avoiding death from starvation had the highest priority, avoiding cardiovascular disease and its consequences (including death as well as other consequences of cardiovascular diseases) was the main aim for the patients in the second half of the last century, and this is still the priority in non-older adults. However, for older people with diabetes, the priority in the management of the disease is to avoid or delay the appearance of functional decline, clinically manifested as frailty and disability (Figure 16.1). This change in priorities is age-dependent and because of that the focus on function should be more relevant for older patients. It should be

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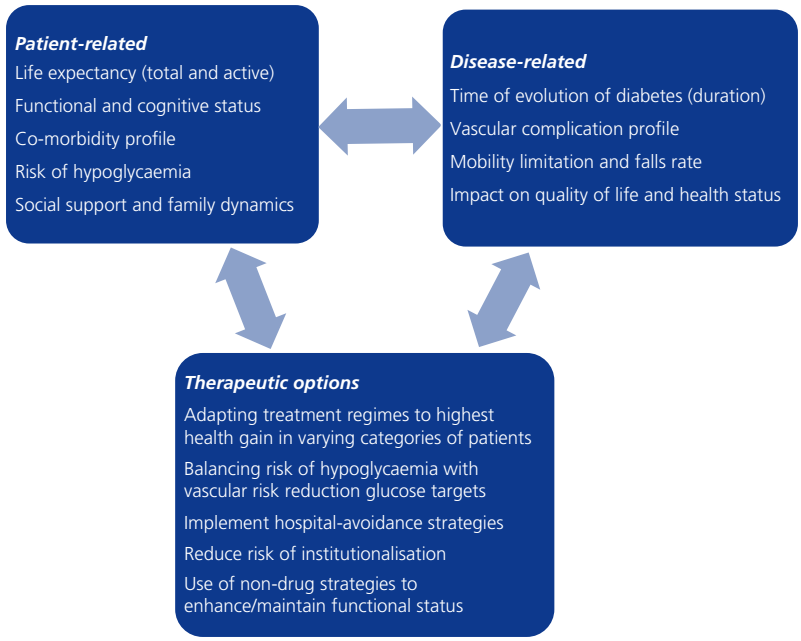

Figure 16.1 Factors affecting treatment decisions and associated therapeutic options [56].

pointed out, however, that putting the focus on functional targets does not mean other targets should be disregarded. In older adults with diabetes the presence of cardiovascular risk factors and cardiovascular disease is, as in non-older adults, more prevalent than in older adults without diabetes, and their risk of death is also higher.

Thus, functional status has a triple meaning in older adults with diabetes: a symptom of the disease, a prognostic marker and a therapeutic goal. The relevance of functional status to clinical practice is so high that it is changing the clinical management of diabetes mellitus in the biggest group of people with diabetes, who represent more than 50% of all people suffering from the disease, older people.

16.2 Functional limitation and diabetes: early background studies

Functional impairment and physical disability directly attributable to diabetes have not been studied in depth, although it has been known for several years that these are direct threats to personal independence and quality of life [1, 2]. A study in older patients with diabetes demonstrated a reduction in physical function and health status in patients with diabetes compared with age- and sex-matched control subjects living in the same community [3]. The increase in functional limitation in diabetes seen in this study is similar to that reported in studies from the USA [4–6] and Hong Kong [7]. There are a number of likely explanations for lower-limb dysfunction in diabetes, such as peripheral neuropathy and peripheral vascular disease. Other important contributors to mobility limitation include age, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), cancer, osteoarthritis, and dementia. However, diabetes itself is known to cause an accelerated loss of muscle, predominantly in the lower limbs [8], and may be associated with an increased falls risk, which may be due in part to diabetes-related complications [9]. Long-duration diabetes also increases the loss of muscle function in older people and this may contribute to the underlying pathophysiological changes in frailty, disability and sarcopenia [10]. Other studies (Box 16.1) have demonstrated that impaired muscle performance may mediate the relationship between type 2 diabetes and slow gait speed in older adults [11], and that severe hyperglycemia and insulin resistance may also be associated with slower walking speed as peripheral neuropathy influences the effect of diabetes on walking performance [12, 13].

Box 16.1 Diabetes and physical function: key references.

The mechanism for impaired physical function in diabetes has been poorly understood: excess physical disability is two to three times more frequent

Volpato S, Ferrucci L, Blaum C, *et al*. Progression of lower-extremity disability in older women with diabetes: the Women's Health and Aging Study. *Diabetes Care* 2003; *26*: 70–5.

Volpato S, Bianchi L, Lauretani F, *et al*. Role of muscle mass and muscle quality in the association between diabetes and gait speed. *Diabetes Care* 2012; *35*: 1672–9.

Diabetes has been associated with muscle atrophy and weakness in different clinical and population-based samples

Park SW, Goodpaster BH, Strotmeyer ES, *et al*. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes* 2006; *55*: 1813–8.

Park SW, Goodpaster BH, Strotmeyer ES, *et al*., Health, Aging, and Body Composition Study. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes Care* 2007; *30*: 1507–12.

CVD, peripheral artery disease, visual impairment, and depression partially explain the association but 60% of excess risk for physical disability remains unexplained

Gregg EW, Mangione CM, Cauley JA, *et al*. Diabetes and incidence of functional disability in older women. *Diabetes Care* 2002; *25*: 61–7.

Maggi S, Noale M, Gallina P, *et al*. Physical disability among older Italians with diabetes. *The ILSA study. Diabetologia* 2004; *47*: 1957–62.

Impaired muscle performance may mediate the association between diabetes mellitus and slower gait speed in older adults, severe hyperglycemia and insulin resistance may also be associated with slower walking speed, peripheral neuropathy influences the magnitude of diabetes on walking performance

Volpato S, Bianchi L, Lauretani F et al. Role of muscle mass and muscle quality in the association between diabetes and gait speed. *Diabetes Care* 2012; *35*: 1672–9.

Kuo CK, Lin LY, Yu YH, *et al*. Inverse association between insulin resistance and gait speed in nondiabetic older men: Results from the US National Health and Nutrition Examination Survey (NHANES) 1999–2002. *BMC Geriatr* 2009; *9*: 49.

Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med* 2007; *167*: 635–41.

De Rekeneire N, Resnick HE, Schwartz AV, *et al*. Diabetes is associated with subclinical functional limitation in nondisabled older individuals: The Health, Aging, and Body Composition Study. *Diabetes Care* 2003; *26*: 1767–72.

16.3 Diabetes and frailty

The pathway from robustness and functional independence toward extreme disability and dependence offers several opportunities for detection and intervention approaches which impede the development or disability. A progressive loss of functional reserve is the pathophysiological fact underlying this pathway, decreasing the capacity to response to injuries and putting the patient at increasing risk of developing disability under the effect of progressively lower stressors, reaching a point where minimal injuries are able to precipitate disability. A second concept to bear in mind is that obtaining any improvement in function requires using part of the available functional reserve. Taking into account the role of these two complementary mechanisms, which explain functional deterioration and the requisite to recover the functional status, it becomes clear that waiting for the development of clinically manifest disability is too late, as the functional reserve will be near absent and the likelihood of improving the functional loss very low. In fact, some studies assessing the probability of recovering functional status to a given stressor (in the case of the study by Boyd *et al*. [14], hospitalization from any cause) have found levels as low as 30% at 1, 3, 6, and 12 months after discharge.

Thus, avoiding functional decline and impairment in these patients demands an active management approach in order to detect those at risk and those in the first stages of the disabling process, where there is still an opportunity (i.e., enough functional reserve) for intervention. In the last few decades an entity able to detect people at risk for disability has been characterized and its main descriptive features, including diagnostic

criteria, defined. This entity, called frailty, can be defined as a situation of extreme vulnerability to the effects of low-intensity stressors. It results from difficulty maintaining homeostasis due to loss of functional reserve [15]. Frailty is a frequent condition, with a prevalence of 10% in people older than 60, reaching 25% in those older than 80 [16]. Frailty is an important predictive factor and because of its reversibility to pre-frailty offers opportunities to avoid or delay incident disability [17]. According to the frailty phenotype, described in 2001 by Linda P. Fried and colleagues [18], an older adult is frail if he/she meets three out of five of the following criteria: loss in weight, low walking speed, low grip strength, low physical activity and fatigability.

The prevalence of diabetes increases with the presence of frailty. The Cardiovascular Health Study (CHS) showed that the prevalence of diabetes was 18.8% in individuals without frailty, 24.5% in individuals with pre-frailty, and 32.4% in individuals with frailty [19]. Likewise, the presence of frailty is higher in patients with diabetes. Data from NHANES and the CHS indicate that frailty is present in 25% of individuals with diabetes and pre-frailty is present in 18.2%, compared with a prevalence of frailty of 6.9% in the whole sample who were aged ≥65 years [18]. Some other studies have found only a slightly higher prevalence of frailty among older adults with diabetes (10.2% of individuals) as compared with older adults without diabetes (7.8%) [20].

As is the case for frailty and disability, the incidence and prevalence of diabetes increase with age, and more than 25% of people aged ≥65 years have diabetes. The International Diabetes Federation (IDF) estimates that 18.6% of people aged between 60 and 79 years have diabetes, and more than 35% of all diabetes cases are in this age group, accounting for 70% of the cost of the disease [21]. In people older than 75 the figure reaches 40% [22] and for those older than 85 the figure is close to 26% [23]. Furthermore, according to the projections from the IDF, by 2035 the number of patients with diabetes will have risen to 590 million. The largest increase is projected among the elderly, with an expected 252.8 million cases at that time. So, in a scenario where the main group of the population, which is going to grow both in relative and absolute terms (people older than 80 years), the coexistence of these two entities (diabetes and frailty) will continue to increase in relevance in the future.

The relationship between diabetes and frailty is noticeably lacking in terms of prospective studies. In this regard, since the seminal study by Barzilay *et al.* [24] first showed an increased risk of frailty in older adults with insulin resistance, there have been several studies showing an association of diabetes with the risk of developing impairments in some of the components of the frailty phenotype, most commonly walking speed [11], but not others, for example grip strength [25]. Another study confirmed the causal association between diabetes and frailty in a cohort study with a mean follow-up of 3.5 years, showing an odds ratio (OR) of 2.18 after adjustment for age, sex, and education level. It is noteworthy that in this study the factors associated with a higher risk of the development of frailty in older people with diabetes were unhealthy behaviors (sedentariness, low physical activity, poor adherence to Mediterranean diet), abdominal obesity, poor glycemic control, and an altered serum lipid profile; in contrast, nutritional therapy and moderate drinking protected against the risk of developing frailty [26]. A study that evaluated the evolution of frailty and pre-frailty in an older cohort living in the community found that the presence of diabetes in women with pre-frailty reduced by 50% the likelihood of improving their frailty status [27].

Since the first studies searching for the relationship between frailty and death in older people it has been shown that frail older patients with diabetes have a higher mortality than non-frail counterparts [28]. This finding is not surprising as frailty is a well-established risk factor for dying [18, 29]. However, the relevance of frailty as a risk factor for death compared with other known risk factors in people with diabetes (mainly cardiovascular diseases) has not been clearly established. In fact, we have unclear evidence about the major specific causes of death in older adults with diabetes [30]. Moreover, a recent study of cardiovascular disease and cancer (including socioeconomic and lifestyle variables) did not account for the excess mortality in older adults with type 2 diabetes [31]. Data from the Toledo Study of Healthy Ageing (TSHA) suggest that frailty, as assessed using the Frailty Trait Score [29] or the Frailty Index [32], is a predominant risk factor for death in older adults with diabetes, even more relevant than co-morbidity (assessed using the Charlson Index) and cardio- or cerebrovascular disease, the two main culprits of increased mortality in the general population of patients with diabetes (Table 16.1).

Table 16.1 Risk of death in older people with diabetes mellitus: after adjustment, only age, sex and frailty remain in the predictive equation.

	Model 1: Risk of death adjusted for age, sex and co-morbidity (Charlson Index)					
	FTS			**FI**		
	HR	**LL**	**UL**	**HR**	**LL**	**UL**
Age	**1.06**	**1.02**	**1.11**	**1.07**	**1.04**	**1.11**
Sex (female)	**0.51**	**0.32**	**0.79**	**0.54**	**0.37**	**0.80**
Charlson Index	1.00	0.89	1.13	0.98	0.88	1.10
Baseline disability	1.29	0.74	2.23	1.09	0.65	1.83
Frailty*	**1.04**	**1.02**	**1.06**	**1.06**	**1.04**	**1.09**
Frailty**	**1.23**	**1.13**	**1.33**	**1.36**	**1.22**	**1.50**
Frailty***	**1.51**	**1.29**	**1.78**	**1.84**	**1.49**	**2.26**
	Model 2: Risk of death adjusted for age, sex and vascular diseases					
	FTS			**FI**		
	HR	**LL**	**UL**	**HR**	**LL**	**UL**
Age	**1.06**	**1.02**	**1.11**	**1.08**	**1.04**	**1.12**
Sex (female)	**0.51**	**0.33**	**0.81**	**0.56**	**0.38**	**0.85**
Baseline disability	1.23	0.71	2.13	1.07	0.63	1.79
Cardiovascular disease	1.45	0.90	2.34	1.37	0.88	2.12
Cerebrovascular disease	0.95	0.49	1.83	0.81	0.45	1.48
Frailty*	**1.04**	**1.02**	**1.06**	**1.06**	**1.04**	**1.08**
Frailty**	**1.22**	**1.13**	**1.33**	**1.35**	**1.22**	**1.50**
Frailty***	**1.49**	**1.27**	**1.76**	**1.83**	**1.49**	**2.24**

FTS, Frailty Trait Score; FI, Frailty Index; HR, hazard ratio; LL, lower limit of 95% confidence interval; UL, upper limit of 95% confidence interval.
* Increase in risk per 1 point of increase in the score.
** Increase in risk per 5 points of increase in the score.
*** Increase in risk per 10 points of increase in the score.
Statistically significant results are shown in bold.

As mentioned already, several factors which are usually present in people with diabetes (hyperglycemia, unhealthy life style, abdominal obesity, high levels of cholesterol and tryglycerides, etc.) appear to be related to the risk of developing frailty in older people with diabetes. However, the mechanisms linking diabetes and frailty are poorly understood. Factors playing a relevant role in the development of complications of diabetes also play a role in the development of frailty, atherosclerosis and vascular dysfunction being the most representative. In addition, other factors, such as depressive illness and cognitive decline [33], may play a relevant role as intermediate factors between diabetes and frailty. Patients with diabetes develop atherosclerosis at an accelerated rate. Atherosclerosis and vascular dysfunction, including endothelial dysfunction, have

been related in epidemiological studies to both the development of frailty and its progression to disability [34–36]. The precise pathways connecting vascular dysfunction and frailty are not fully understood but processes that affect muscle performance (i.e., peripheral vascular disease and peripheral neuropathy) or chronic kidney disease, which can result in inactivity, loss of muscle mass, and a decline in physical and cognitive function, seems to be involved [33, 37]. Diabetes and depression are inter-related, and depression has been linked to a progressive decline in strength. It has also been shown that diabetes and impaired glucose tolerance are associated with a worsening of cognitive function. Patients with type 2 diabetes are at an increased risk of developing mild cognitive impairment, vascular dementia, and Alzheimer's disease. Additionally, elevated glucose levels have been associated with an increased risk of developing dementia in patients without diabetes [38]. Hypoglycemia may also affect the risk of developing frailty in older adults with diabetes, which in turn places the patient at a higher risk of suffering new episodes of hypoglycemia [39].

These mechanisms provide pathways linking diabetes and frailty, and could explain part of frailty's attributable risk of an adverse event in older patients with diabetes. However, the main factor explaining this link is in fact sarcopenia (Figure 16.2). Sarcopenia, the progressive loss of muscle mass and strength, has been identified as a common pathway associated with the initial onset and progression of physical disability among older adults. A growing body of evidence suggests that metabolic dysregulation associated with obesity and diabetes accelerates the progression of sarcopenia and subsequently functional decline in older adults [40, 41].

16.4 Diabetes and disability

Disability, in its different degrees of severity, is the final stage for the pathway leading from robustness and an independent life towards severe disability, high dependency, and a dependent life. Thus, many of the concepts that have been described when talking about diabetes and frailty also are operative for disability.

Early clinical studies published at the end of the last century showed some cross-sectional relationship diabetes and disability [42–44]. This finding was confirmed in many other cross-sectional studies and in one case-control study [3] over the next decade [45]. In 2002, prospective data from the Osteoporotic Fracture Study was published showing an association between having diabetes and the risk of developing disability in mobility (walking, climbing stairs and doing housework) in women followed up for 9 years [46]. Other studies showed a deleterious effect of diabetes on incident disability for both basic and instrumental activities of daily living (IADL) [47, 48]. If we collate this evidence it is clear that diabetes in older adults increases the risk of mobility disability (OR 1.71 RR 1.51), IADL disability (OR 1.65), and activities of daily living (ADL)

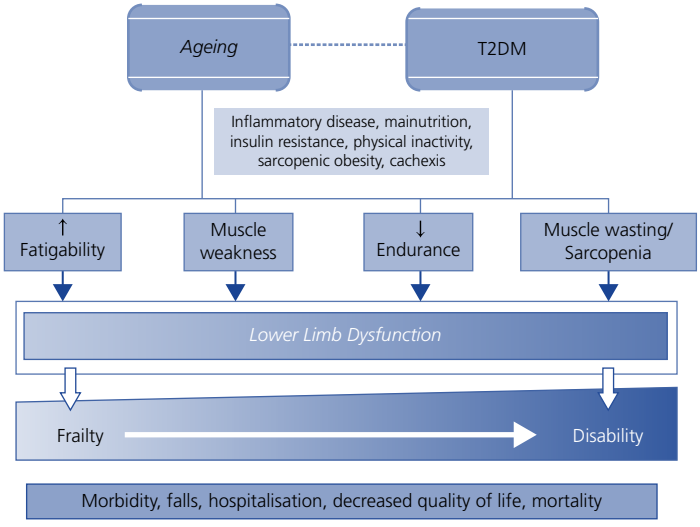

Figure 16.2 Ageing and diabetes sarcopenia: relationship with lower limb performance [41]. T2DM, type 2 diabetes mellitus.

disability (OR 1.82, RR 1.82) [45]. It must also be said that this effect of diabetes on disability has recently also been shown in very old (>84 years) after a follow-up of 2 years [23]. In this same regard it is noteworthy that the time for developing functional impairment is not long. In fact, most studies have shown this effect in a period of time shorter than 2 years. This is important as it shows that the functional impairments of diabetes can happen inside the usual life expectancy of older people.

There are also some data illustrating the risk associated with diabetes of developing impaired cognitive function, which is considered to be another pillar of disability. Diabetes is associated with both mild cognitive impairment and dementia. Several deficits in neuropsychological function in diabetes subjects have been demonstrated: mental and motor slowing and decrements of similar magnitude on measures of attention and executive functioning [49]. Both hyperglycemia and hypoglycemia appear to increase the risk of dementia [38, 50].

Regarding factors which explain the development of disability in older adults with diabetes, it would appear reasonable to suggest that they are same ones that are involved in the other associated sequelae. However, data from the Italian Longitudinal Study of Aging (ILSA) [51] has shown that traditional damage due to diabetes (macro- and microvascular disease, diabetic neuropathy) accounted for less than 40% of the incident disability. This introduced the likelihood of other factors, including sarcopenia and cognitive impairment, being involved in the development of functional impairment in older adults with diabetes.

16.5 Functional assessment in varying clinical sectors

Functional status is an important prognostic factor in older patients, including those with diabetes. Furthermore, recent data from the TSHA study showed that frailty is the most important predictor of death in older adults with diabetes, emphasizing the importance of the functional assessment of these patients. Consequently, as recommended by the IDF and treatment guides for older people with diabetes [52, 53], multidimensional and, whenever possible, multidisciplinary assessments of older patients with diabetes should be performed to collect information about the medical, functional, cognitive, emotional, and social functioning of the patient, and this information should be a critical part of the clinical evaluation of older patients with diabetes. The benefits of this assessment in the context of diabetes mellitus are summarized in Table 16.2.

Table 16.2 Benefits of comprehensive geriatric assessment.

Assesses the life expectancy.
Assesses the likelihood of benefit from different interventions and treatments.
Assesses the likelihood of suffering complications of the disease.
Provides a measure of the patient's ability to meet the treatment goals and to follow dietary recommendations.
Assesses the capacity for self-care and self-management of the disease.
Assesses the impact of vascular complications of diabetes, including peripheral vascular disease or neuropathy.
Assesses the risk of adverse drug reactions.
Assesses the need for support.
Identifies aspects of quality of life related to the disease or its treatment.
Provides the information needed to design an integrated management plan.

The Comprehensive Geriatric Assessment (CGA) is an objective, measurable, easy-to-implement and the most useful tool to define functional characteristics in older people. This assessment is a dynamic and structured diagnostic process that detects and quantifies the problems, needs, and abilities of the older individual in four key areas: clinical, functional, mental, and social. This assessment can then be used to develop an interdisciplinary plan for intervention, treatment, and long-term monitoring, thereby enabling the patient to maintain a high degree of independence and an acceptable quality of life. During this evaluation, emphasis should be placed on managing these complex diseases and evaluating the patient's quality of life. At a minimum, the evaluation should assess the patient's functional capacity, cognitive function, and mental health.

The frequency, extension, and depth of CGA in each patient depend on two main factors: the characteristics of the patient and the care setting. For instance, chest pain is assessed in different ways in a young woman, a middle age man with cardiovascular risk factors, and a

patient who has suffered a myocardial infarction or been submitted to a triple coronary bypass. In addition, the assessment will be different in a community setting and an emergency room or coronary care unit. CGA should generally be done in every older adult with diabetes at the time of diagnosis and annually thereafter. In some populations at high risk of functional decline and in some settings, more frequent assessment is recommended. Factors that require assessment include presence of delirium, depression, falls, incontinence, mobility problems, pressure ulcers or functional impairment, admission to and recent discharge from a hospital, recent admission to a nursing-home, polypharmacy, disability due to vascular disease or neuropathy requiring a rehabilitation program.

The recommendation about functional assessment has been recently reinforced regarding frailty. According to the international consensus on frailty "all persons aged 70 years or older, as well as any person with a significant weight loss (≥5% over the past year) due to chronic illness should be screened for frailty" [54]. Given the significant repercussions that frailty has on older individuals (especially patients with diabetes), and the implications for the management of diabetes, the IDF also recommends screening patients with diabetes who are aged ≥70 years for frailty.

Several national and international bodies [52, 54, 55] have made recommendations about the set of instruments to be used when assessing functional status (including frailty) in older adults with and without diabetes mellitus. Table 16.3 lists a number of instruments that can be used to assess function. All these instruments, when used prospectively, are very useful for monitoring any evidence of functional decline.

Finally, and in addition to the functional assessment of older adults with diabetes, it is sensible to make some recommendations on how to screen and diagnose diabetes in frail and disabled older people. Given the elevated prevalence of diabetes in older patients, especially those who are frail or disabled, and because approximately 40% of cases of diabetes remain undiagnosed [22], all older patients should be periodically evaluated to detect diabetes. These evaluations are especially warranted in certain groups, including in

Table 16.3 Instruments for evaluating frailty and its components and/or associated areas.

Dimension	Instrument
Frailty	• Fried Frailty Phenotype • Frailty Index • 7-point Clinical Frailty Scale • 9-point Clinical Frailty Scale[a] • Frailty Trait Scale • FRAIL Screening Questionnaire • Groningen Frailty Indicator • Tilburg Frailty Indicator [57] • The Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI)
Functional decline (performance-based)	• Short Physical Performance Battery (SPPB) • Timed up and go (TUG) test • 4-m gait speed test • Institute for Diabetes in Old People (IDOP) three-steps package[†] (walking/balance/mobility)
Disability	• For basic activities of daily living: Barthel Index[a]/Katz Index • For instrumental activities of daily living: Lawton and Brody Scale
Cognitive and emotional assessment	• Mini Mental State Examination: Folstein • MiniCog or Montreal Cognitive Assessment Tool (MoCA)[a] • Pfeiffer Scale (Portable Functional Assessment Questionnaire) • Yesavage Geriatric Depression Scale[a]

[a] Tools recommended by the International Diabetes Federation for the management of the older patient with type 2 diabetes [52].

Table 16.4 Future research questions: diabetes and functional limitation.

Research	How to address gaps/shortfalls in the field
Exploring the role of frailty state and sarcopenia in the etiology of a functional decline in diabetes	• Examining the interplay between frailty, sarcopenia and vascular/non-vascular co-morbid illness in diabetes • Testing a series of frailty functional assessment scales in people with early mobility limitation • Identification of sarcopenia and frailty in new-onset diabetes and in long-duration diabetes
Applicability of personalized support systems/ assistive technology in routine clinical practice	• Feasibility/pilot assessments of electronic decision support tools (aids) • RCTs of their effectiveness in mobility limitation and prevention of disability
Developing clinical trial methods: influencing government bodies, medical charities and major pharma to participate	• RCTs in older people (>75 years) to examine the benefits of glucose regulation using outcome measures such as pre-disability/disability, incidence of dementia, frailty, quality of life, mood level, hypoglycemia and hospitalization rates • Demonstration of likely benefits in a broad range of older people with diabetes: frail, care home residency/housebound, dementia, and end-of-life care
Influencing commissioners of clinical diabetes services	• Health economic analyses of interventions using study designs that allow relevant and appropriate cost comparisons • Employ analytical methods that account for biases such as confounding due to co-morbid illness

RCT, randomized clinical trial.

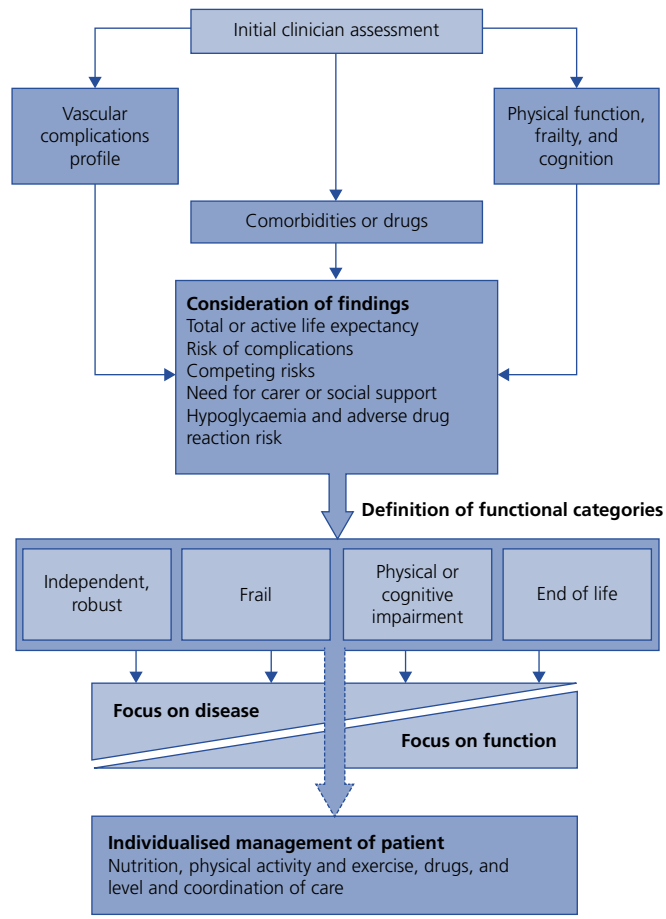

Figure 16.3 The management of diabetes in older people.

all patients admitted to a nursing home. The IDF recommends using the same diagnostic criteria for diabetes that are used for the general population, but only the simplest possible tests should be used in frail patients.

16.6 Conclusions

Diabetes can contribute to frailty by increasing the incidence of many of the core components of frailty (weakness–strength impairment, exhaustion, slowness and low physical activity level) or through some of the co-morbidities and complications associated with this condition (atherosclerosis, microvascular complication, cardiovascular autonomic neuropathy or peripheral neuropathy or dementia/cognitive impairment).

Further research (Table 16.4) should provide a clearer insight into these inter-relationships and may help to confirm the complexity of managing diabetes in older people (Figure 16.3).

Detection of frailty, functional decline, and functional impairment should be a prompt to the physician to review management aims and goals [57]. Accordingly, early recognition of frailty and sarcopenia in older adults with diabetes should be a mandatory process to promote early multi-modal interventions based on physical exercise and nutritional education, and align with glycemic and other metabolic targets essential to proper functioning.

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CHAPTER 17

Metabolic decompensation in older people

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KEY MESSAGES

- Impaired glucose homeostasis in aged individuals may vary from light, often unrecognized, hyperglycemia to acute hyperglycemic crisis, both of which are frequent causes of hospital admission.
- The attainment of appropriate glycemic control to reduce acute complications associated with diabetes is a priority for all older people
- Hypoglycemia in the older subject can have serious, sometimes life-threatening, consequences for the heart or brain, in terms of both morbidity and quality of life.
- Hypoglycemia is three times more frequent when insulin is used alone compared with antidiabetic drugs, with combined treatments exposing the patient to an intermediary risk.
- The mortality rate of hyperosmolar hyperglycemic state (HHS) has remained high at ~15%, compared to less than 5% in patients with diabetic ketoacidosis (DKA).
- In both DKA and HHS, the underlying metabolic abnormality results from the combination of absolute or relative insulin deficiency and increased amounts of counter-regulatory hormones.
- Many features of DKA and HHS predispose the patient to thrombosis, including dehydration and contracted vascular volume, a low cardiac output, increased blood viscosity, and the frequent presence of underlying atherosclerosis.
- The therapeutic goals for treatment of hyperglycemic crises consist of improving the circulatory volume and tissue perfusion, decreasing serum glucose and plasma osmolality toward normal, clearing serum and urine of ketones at a steady rate, correcting electrolyte imbalances, and identifying and treating precipitating events.

17.1 Introduction

Impaired glucose homeostasis plays a role of importance in aged individuals, its manifestations varying from light, often unrecognized, hyperglycemia to acute hyperglycemic crises, both of which are frequently causes of hospital admission.

Hyperglycemic complications include dehydration, mental status changes, increased risk of infection, and, in severe cases, the possibility of ketoacidosis and hyperosmolar coma, a condition more often fatal in the elderly. In the elderly, the mortality rate for diabetic emergencies associated with ketoacidosis remains low. By contrast, the mortality rate for diabetic emergencies associated with a hyperosmolar state remains considerably higher.

The attainment of appropriate glycemic control to reduce acute complications associated with diabetes is a priority for all older people. Although flexibility may be allowed in setting glycemic parameters for individual treatment goals, the clinician also must take into account the need to prevent associated acute complications.

Not only higher glycemic values, but also, and even more dangerous, hypoglycemic episodes can disturb the frail equilibrium of older patients. Achieving target glycemic goals while avoiding hypoglycemia is a major

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challenge in the management of elderly patients with diabetes mellitus. Repeated episodes of hypoglycemia may cause extreme emotional distress in such patients, even when the episodes are relatively mild.

17.2 Hypoglycemia

Hypoglycemia accounts for a relatively high number of emergencies requiring hospital admission. Results from a large retrospective observational study using data from Medicare fee-for-service beneficiaries 65 years or older demonstrated that hospital admission rates for hypoglycemia exceeded those for hyperglycemia among older adults [1, 2]. Between 1999 and 2011, as glycemic control in the US population with diabetes mellitus improved [3], hyperglycemic events requiring hospital admission declined among older adults, but severe hypoglycemic events requiring hospitalization increased. Throughout this 12-year period adults 75 years or older experienced much higher rates of hypoglycemia leading to admission than those 65–74 years old. The 1-year mortality rate after a hypoglycemia admission was higher (22.6%) than the rate after a hyperglycemia admission (17.6%) in 2010 [1]. Estimated rates of admissions among older adults with diabetes mellitus using additional data from the Behavioral Risk Factors Surveillance System (BRFSS) showed an even more dramatic decline in hyperglycemia hospitalizations but also a slight decrease in hypoglycemia hospitalizations over time [1]. These results show considerable progress in reduction of admissions for hyperglycemia that has not been matched by similar advances in prevention of admissions for hypoglycemia.

In older patients, susceptibility to hypoglycemia is pronounced and is exacerbated by older people having little knowledge about the symptoms and signs of hypoglycemia [4, 5]. While hypoglycemic events are usually of minor importance, in some instances death or severe sequelae, including myocardial infarction and stroke, may occur.

Hypoglycemia in the elderly subject can have serious, sometimes life-threatening, consequences for the heart or brain, in terms of both morbidity and quality of life [6]. Some patients may have permanent neurological damage, presumably because of an already compromised cerebral circulation [5]. Hypoglycemic events in the elderly are independently associated with an increased risk of fall-related fractures and acute cardiovascular events [7]. These events have been shown to adversely impact health-related quality of life as much as, or to an even greater degree than, complications of type 2 diabetes mellitus [8–10].

Furthermore, evidence suggests that severe hypoglycemic episodes may increase the risk of dementia in patients with type 2 diabetes mellitus [11]. Thus, in older subjects, the risk of hypoglycemia must be evaluated as clearly as possible and balanced, on an individual basis, against the potential benefit of a near-normal glucose level.

Symptomatic hypoglycemia can be distinguished from "silent" hypoglycemia, which is frequently associated with the occurrence of severe hypoglycemia [12]. Symptoms are somewhat different than those observed in younger subjects (especially blurred vision and instability) and often blunted by an autonomous neuropathy or impaired cognitive function ("silent" hypoglycemia). Hypoglycemic symptoms in the elderly tend to present predominantly as neuroglycopenic symptoms: impaired concentration, personality changes, focal neurologic deficits, seizure or syncope. Nocturnal hypoglycemia may present as morning headaches or disturbed sleep. Adrenergic symptoms (tremulousness, anxiety, diaphoresis, palpitation, and hunger) are diminished in part due to a loss of autonomic nerve function [13, 14]. Glucose counter-regulatory hormones, such as glucagon, epinephrine, and growth hormones (GHs), are the most important hormones secreted in response to hypoglycemia. When glucagon is deficient, epinephrine becomes critical. Growth hormone and cortisol are important if hypoglycemia is prolonged [15]. The elderly exhibit an impaired response of glucose counter-regulatory hormones in the presence of decreased glucose. Furthermore, the rate of insulin clearance from the circulation declines with age, which may enhance the risk of hypoglycemia in elderly people [16–18].

Alterations in the release of counter-regulatory hormones could increase the susceptibility of the elderly to hypoglycemia. Early studies of the effect of age on counter-regulatory hormone responses to hypoglycemia produced inconsistent results [19, 20]. These studies were flawed because many of the elderly subjects studied suffered from underlying diseases. Recent studies that have carefully selected older subjects to be free from disease have found that healthy elderly

subjects have impaired glucagon responses to hypoglycemia [21, 22]. Epinephrine responses have been reported to be impaired [21] or increased in the healthy elderly [13]. Cortisol responses have been found to be normal [21] or increased [22], and GH responses may be impaired [21], although this has not been demonstrated conclusively.

A reduced epinephrine response to hypoglycemia and a decreased responsiveness to α-adrenergic receptor stimulation may explain the reduced awareness of the autonomic symptoms of hypoglycemia found in the healthy elderly when compared to young subjects [23]. In young adults, symptomatic responses to hypoglycemia are generated at a blood glucose level that is higher than the level at which cognitive function becomes impaired. This allows sufficient time to take corrective action before severe neuroglycopenia supervenes [24]. The difference between these glycemic thresholds is ~ 1.0 mmol/l (18 mg/dl). Indeed, in older persons the difference between the glycemic threshold for subjective awareness of hypoglycemia and that for the onset of cognitive dysfunction may be absent [25]. Thus, elderly patients who became hypoglycemic are less likely to experience prior warning symptoms if blood glucose falls and are at greater risk for injury or falls with fracture, all factors which have a disruptive effect on the frail subject. However, two recent studies described less serious consequences in elderly subjects who are given adequate care: mortality was zero in a study from Germany [13] and morbidity was 4% in a study from Singapore [4]. Furthermore, elderly diabetics are not more exposed to car accidents [13], a serious complication of hypoglycemia observed in the young population of the Diabetes Control and Complications Trial (DCCT) [12].

Hypoglycemia is usually observed at the end of the morning and in the afternoon in insulin-treated patients. Favoring factors other than age are multiple co-morbid conditions (psychiatric conditions and depression leading to variable food intake), renal impairment (sulfonylureas multiply the risk of severe hypoglycemia by nine, especially if food intake is irregular), multiple medications (high-risk association with antibacterial sulfonamides), and more frequent poorly adapted behavior response. To this list should be added the rare use of self-monitoring and the absence of patient and caregiver education regarding the symptoms of hypoglycemia. Furthermore, the direct cause of hypoglycemia is generally related to a dietary error (53% of hypoglycemic episodes follow a skipped meal) and/or recent hospitalization (change in therapy poorly adapted to home life) [5], African American race, and use of five or more concomitant medications [26, 27]. The frequency of severe hypoglycemia remains moderate among patients with type 2 diabetes (0.4 episodes per 100 patient-years), irrespective of treatment, compared with insulin-treated patients (1.5 episodes per 100 patient-years) [5].

Hypoglycemia occurs by far more frequently as a consequence of inadequate therapy in diabetes management, as was demonstrated in the DCCT and the United Kingdom Prospective Diabetes Study (UKPDS) [12, 28]. The frequency of hypoglycemic episodes increases with increasing quality of glycemic control assessed with HbA1c. Older patients, particularly those with multiple co-morbidities, may derive less benefit from intensive strategies to lower glucose levels [12] and may be more susceptible to hypoglycemia [13] and its consequences. It is generally accepted that hypoglycemia occurs when the capillary blood glucose level is below 0.6 g/l.

The International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People, and the International Task Force of Experts in Diabetes published a position statement in 2012 on the management of diabetes in older adults, explicitly addressing the need to avoid hypoglycemia [29]. In general, an HbA1c target range of 7.0–7.5% should be set, but a more precise goal based on clinical characteristics may need to be recommended. To reduce the risk of hypoglycemia, no patient should have an on-treatment fasting blood glucose (FBG) level of less than 6.0 mmol/l (108 mg/dl), and blood glucose levels below 5 mmol/l (90 mg/dl) should be strictly avoided. Furthermore, glucose-lowering therapy should not be initiated unless the FBG level is consistently above 7 mmol/l (126 mg/dl) [29]. The hypoglycemic risk associated with antidiabetic agents represents the greatest barrier to optimal glycemic control in elderly patients [30], therefore diabetes therapies with the lowest rates of hypoglycemia should be considered for this patient population [31].

For oral antidiabetic drugs, α-glucosidases and metformin do not usually cause hypoglycemia. The pharmacokinetic properties of sulfonamides favors the use of second-generation short-acting drugs. Unlike conventional sulfonylureas, glinides taken before a meal induce a rapid post-prandial insulin response.

The short half-life of these drugs ensures that insulin concentrations peak at 1–2 h and by 6 h are back at fasting concentration with little risk of hypoglycemia if the patient misses a meal, which is, on the other hand, a severe problem with the old sulfonylureas. A support to such clinical evidence comes from studies showing the risk of severe hypoglycemia to be less than half that seen with traditional sulfonylureas [32]. The short half-life and biliary elimination of glinides are interesting properties, but like glitazones, specific large-scale studies in elderly persons are lacking.

Recent developments in incretin-based therapies and long-acting insulin analogs demonstrate lower hypoglycemia risk than traditional therapies such as sulfonylureas and human insulin [33]. Among the currently available incretin-based therapies, the dipeptidyl peptidase-4 (DPP4) inhibitors, sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin have been confirmed to be well tolerated in older adults with few gastrointestinal side effects and little effect on body weight, with similar efficacy as younger adults, and can be safely used in renal insufficiency with labeled dose adjustment for each drug [34–38]. DPP4 inhibitors resulted in reductions in HbA1c for patients whose baseline HbA1c levels were higher [37]. This excellent tolerability profile, low risk of hypoglycemia, and once-daily dosing make this drug class suitable for frail and debilitated elderly patients [31].

Glucagon-like peptide 1 (GLP-1) receptor agonists are also effective in glycemic control and are well tolerated without increasing the risk of hypoglycemia in older patients [39, 40]. In addition to their glucose-lowering effects, GLP-1 receptor agonists delay gastric emptying and increase satiety, resulting in weight loss, in particular reductions in subcutaneous fat mass [41].

Hypoglycemia is three times more frequent when insulin is used alone compared with anti-diabetic drugs, with combined treatments exposing the patient to an intermediary risk. Advances in molecular genetic engineering have made possible the development of insulin analogues with pharmacokinetics that more closely mimic the needs of patients with type 2 diabetes, reducing the risk of hypoglycemia. LysPro insulin and insulin aspart, which are rapid-acting insulin analogues, administered immediately prior to a meal have demonstrated improved post-prandial glucose control in comparison with regular insulin. Injection just before meals, or even during meals, is a good way of adapting the dose to real food intake, but in practice multiple injections are not always easy to implement in the elderly subject [27, 42–44]. The long-acting insulins degludec, glargine, and detemir are safer choices than NPH in older adults because of their lower risk of hypoglycemia, especially nocturnal hypoglycemia, which may contribute to cardiovascular morbidity and falls [45–49]. Insulin degludec resulted in less hypoglycemia than insulin glargine even in long-duration diabetic patients, whose counter-regulatory hormone responses were presumed to be weaker [46].

In conclusion, older people with type 2 diabetes suffer a higher frequency of hypoglycemic episodes; the highest frequency and the most severe hypoglycemia is observed in insulin-treated patients. Particular at-risk situations are chronic renal failure and polymedication, which are often present in this population. Prescription of long-acting sulfonylureas is not recommended in elderly patients. Targeting "perfect" glycemic control, which is associated with a significant hypoglycemic risk, is not justified in many elderly patients. In patients over 65 years, recommended therapeutic targets for glycemic control should be fixed at a higher level than in younger patients. To prevent severe if not even fatal hypoglycemia in older patients, careful insulin scheduling, when necessary, should include preparations characterized by shorter half-life and minimal risk for nocturnal episodes. The short half-life sulfonamides, metformin, incretin-based therapies, and molecules tolerated in renal and liver function impairment should be the first choice for geriatric care. Future research is needed to explore the best combination of antidiabetic therapies for achieving glycemic control in elderly patients safely and effectively.

Finally, due to the fact that elderly patients are often incapable of treating hypoglycemia themselves, educational programs should include advice and information relating to the detection and treatment of hypoglycemia, including the criteria for hospital admission in cases of unresponsive hypoglycemia [50].

17.3 Diabetic ketoacidosis and hyperosmolar hyperglycemic state in the elderly

Diabetic ketoacidosis (DKA) and hyper-osmolar non-ketotic coma (HONK) are two of the most serious acute complications in the spectrum of marked decompensated diabetes [51–54].

These hyperglycemic emergencies persist as important causes of morbidity and mortality among diabetic patients despite major advances in the understanding of their pathogenesis and more uniform agreement about their diagnosis and treatment. In contrast to DKA mortality, the mortality rate of hyperosmolar hyperglycemic state (HHS) has remained high at ~15%, compared to less than 5% in patients with DKA [27, 55–57]. Severe dehydration, older age, and the presence of co-morbid conditions in patients with HHS account for the higher mortality in these patients [57].

DKA consists of the biochemical triad of hyperglycemia, ketonemia, and metabolic high-anion gap acidosis [55]. The terms "hyperglycemic hyperosmolar nonketotic coma" and "hyperglycemic hyperosmolar nonketotic state" have been replaced with the term "hyperglycemic hyperosmolar state" to reflect the fact that (1) alterations of the sensoria may often be present without coma and (2) the hyperosmolar hyperglycemic state may consist of moderate to variable degrees of clinical ketosis [52].

Although DKA most often occurs in patients with type 1 diabetes mellitus, it may also occur in type 2 diabetes under conditions of extreme stress such as serious infection, trauma, and cardiovascular or other emergencies. Less often, it will present as a manifestation of type 2 diabetes, a disorder called ketosis-prone type 2 diabetes [56]. Similarly, whereas HHS occurs most commonly in type 2 diabetes mellitus, it can be seen in type 1 diabetes mellitus in conjunction with DKA [58, 59]. While DKA and HHS are characterized by absolute or relative insulinopenia, clinically they differ only by the severity of dehydration, ketosis, and metabolic acidosis [60, 61].

Both DKA and HHS can be seen in the elderly [62]. DKA is rare and its features and management do not differ from those in younger diabetics. However, its mortality is greatest in old age, particularly because of associated cardiovascular disease [62, 63] (Table 17.1). Older patients are less likely to be on insulin before developing DKA, less likely to have had a previous episode of DKA, typically require more insulin to treat the DKA, have a longer length of hospital stay, and have a higher mortality rate (22% for those aged ≥65 versus 2% for those aged <65) [62]. Causes of death include infection, thromboembolism, and myocardial infarction [62]. Although concomitant diseases and high rates of morbidity must be considered when caring for older patients with DKA, no specific treatment guidelines are currently available.

Table 17.1 The main features of diabetic ketoacidosis (DKA) and hyperglycaemic state (HHS) in older people.

DKA

1 Rare in the elderly.
2 Patient less likely to be on insulin before developing DKA.
3 Patient less likely to have had a previous episode of DKA.
4 More insulin required to treat the DKA.
5 A longer length of hospital stay.
6 Higher mortality rate.
7 No specific treatment guidelines are available.

HHS

1 Occurs frequently in the elderly.
2 In 50% of cases diabetes mellitus has not been previously diagnosed or treated.
3 Frequent predisposing factors are:
  a impaired maintenance of serum osmolality
  b decreased thirst perception (especially in elderly with dementia)
  c decreased access to water, especially in the bedridden and with use of diuretics
  d acute infection (pneumonia being the most common infection).
4 Symptoms, signs, diagnosis, and treatment are otherwise similar to those in younger adults.

HHS almost always occurs in older people, and in about half of the cases diabetes mellitus has not been previously diagnosed or treated [64]. The predisposition of the elderly to develop HHS can be explained by a combination of impaired maintenance of serum osmolality, decreased thirst perception (especially in elderly with dementia), and decreased access to water, especially in the bedridden and with the use of diuretics. A reduced thirst perception renders the polydipsia less dramatic, thereby lessening recognition by self or others, leading to dehydration and ending in hyperosmolar coma [65]. An acute infection is the most frequent predisposing factor (40–60%), with pneumonia being the most common infection. Other illnesses such as stroke, acute myocardial infarction, renal insufficiency, and medications such as glucocorticoids can also be predisposing factors. The symptoms, signs, diagnosis, and treatment are otherwise similar to those in younger adults.

17.4 Pathogenesis of DKA and HHS

In both DKA and HHS the underlying metabolic abnormality results from the combination of absolute or relative insulin deficiency and increased amounts of

counter-regulatory hormones. Inadequate levels of circulating insulin lead to hyperglycemia, which in turn can lead to progressive dehydration and hyperosmolarity, and ultimately to HHS. If the insulin deficiency is severe enough, ketosis and ultimately acidosis develop. A relative insulin deficiency – not absolute insulin deficiency – is necessary for the development of both DKA and HHS. Even patients with type 2 diabetes mellitus and "normal insulin levels" may develop DKA if the levels of insulin resistance cause a sufficiently large increase in insulin requirement.

When insulin is deficient, the elevated levels of glucagon, catecholamines, and cortisol will stimulate hepatic glucose production through increased glycogenolysis and enhanced gluconeogenesis [55]. Hypercortisolemia will result in increased proteolysis, thus providing amino acid precursors for gluconeogenesis.

Low insulin and high catecholamine concentrations will reduce glucose uptake by peripheral tissues. The combination of an elevated hepatic glucose production and decreased peripheral glucose utilization is the main pathogenic disorder responsible for hyperglycemia in DKA and HHS. The hyperglycemia will lead to glycosuria, osmotic diuresis, and dehydration. Initially, glycosuria causes an increase in the glomerular filtration rate (GFR), but when the hypovolemia becomes significant, the GFR is decreased and renal glucose losses may decrease. As glucose clearance by the kidney declines, the hyperglycemia and hyperosmolarity worsen.

In DKA, the low insulin levels, combined with increased levels of catecholamines, cortisol, and GH, will activate hormone-sensitive lipase. This causes the breakdown of triglycerides and release of free fatty acids (FFAs). The FFAs are taken up by the liver and converted to ketone bodies that are released into the circulation. This process of ketogenesis is stimulated by the increase in glucagon levels [66]. Glucagon will activate carnitine palmitoyltransferase I, an enzyme that allows FFAs in the form of coenzyme A to cross mitochondrial membranes after their esterification into carnitine. On the other hand, esterification is reversed by carnitine palmitoyltransferase II to form fatty acyl coenzyme A, which enters the β-oxidative pathway to produce acetyl coenzyme A. Most of the latter is utilized in the synthesis of β-hydroxybutyric acid and acetoacetic acid, two relatively strong acids that are responsible for the acidosis in DKA.

Normally, ketone bodies increase insulin release from the pancreas and the insulin in turn suppresses ketogenesis. In the insulin-deficient state, however, the pancreatic β-cells are unable to respond and ketogenesis proceeds unchecked.

The reason for the absence of ketosis in the presence of insulin deficiency in HHS remains unknown (52). The current hypothesis is that the absence may be due to lower levels of FFAs or higher portal vein insulin levels, or both [51, 67, 68]. It appears that in hyperglycemic coma most subjects with type 2 diabetes have just enough residual insulin secretion to suppress lipolysis and ketogenesis, thus avoiding DKA and developing a HONK coma instead. However, in one study similar insulin levels were found in subjects with DKA or HONK, whereas those with HONK had lower levels of counter-regulatory hormones, leading to less lipid breakdown and less hepatic ketogenesis [69]. It also appears that hyperosmolality not only worsen insulin resistance but also inhibits lipolysis [70].

17.4.1 Acid–base balance, fluids, and electrolytes

Acidosis in DKA is due to the overproduction of β-hydroxybutyric acid and acetoacetic acid. At physiological pH, these two ketoacids dissociate completely, and the excess hydrogen ions bind the bicarbonate, resulting in decreased serum bicarbonate levels. Ketone bodies thus circulate in the anionic form, which leads to the development of anion gap acidosis that characterizes DKA. Despite substantial losses of ketoacids in the urine, the decrease in serum bicarbonate concentration and the increase in the anion gap observed in DKA are about equal [71]. Metabolic acidosis will induce hyperventilation through a stimulation of peripheral chemoreceptors and the respiratory center in the brainstem, which will elicit a decrease in the partial pressure of carbon dioxide. This will partially compensate for the metabolic acidosis.

Hyperglycemia-induced osmotic diuresis results in severe fluid loss. The total body deficit of water is usually about 5–7 l in DKA and 7–12 l in HHS, which represents a loss of about 10–15% of body weight. The osmotic diuresis is associated with large losses of electrolytes in the urine. The sodium chloride deficit in DKA and HHS is usually 5–13 mmol/kg of body weight for sodium and 3–7 mmol/kg for chloride [52, 55, 67]. Initially, increased glucose concentration is restricted to the extracellular

space, which forces water from the intracellular to the extracellular compartment and induces a dilution of the plasma sodium concentration. Subsequently, further increases in the plasma glucose concentration will lead to osmotic diuresis, with losses of water and sodium chloride in the urine; the water loss usually exceeds that of the sodium chloride [55, 71].

Because of the osmotic shift of water, plasma sodium concentrations are usually low or normal in DKA and can be slightly increased in HHS, despite extensive water loss [71, 72]. In this context, the plasma sodium concentration should be corrected for hyperglycemia by adding 1.6 mmol to the reported sodium level for every 5.6 mmol/l increase in glucose above 5.6 mmol/l [55]. The plasma sodium concentration may also be artificially lowered by the presence of severe hyperlipidemia.

Both DKA and HHS are also associated with profound total body potassium depletion, ranging from 3 to 15 mmol/kg of body weight [53, 67, 73]. However, plasma potassium concentrations are typically normal or elevated at the time of presentation. As with sodium, the presence of hyperglycemia leads to a shift of water and potassium from the intracellular to the extracellular space. The shift of potassium is further enhanced in the presence of acidosis, intracellular proteolysis, and insulinopenia [74]. Potassium depletion is due to excessive urinary potassium loss secondary to osmotic diuresis, and it leads to increased delivery of fluid and sodium to potassium secretory sites in the distal nephron [55]. This can be further exacerbated by poor oral intake of potassium, vomiting, and secondary hyperaldosteronism [55].

Phosphate, magnesium, and calcium are other elements excreted in excess in urine during the development of DKA and HHS owing to osmotic diuresis, for a deficit of 1–2 mmol/kg on average [53, 67].

17.4.2 Precipitating factors

Infection remains the most important precipitating factor in the development of DKA and HHS. In 20–25% of cases, infections are the first manifestations of previously undiagnosed diabetes mellitus [74]. Omissions or inadequate insulin doses are frequent precipitating factors, particularly for DKA [67].

Other precipitating factors, especially for HHS, are silent myocardial infarction, cerebrovascular accident, mesenteric ischemia, acute pancreatitis, and use of medications such as steroids, thiazide diuretics, calcium-channel blockers, propranolol, and phenytoin [52]. In 2–10% of cases of DKA, no obvious precipitating factor can be identified [74].

17.5 Diagnosis of DKA and HHS

17.5.1 Clinical presentation

If physical examination reveals dehydration along with a high capillary blood glucose level with or without urine or increased plasma ketone bodies, than acute diabetic decompensation should be strongly suspected. A definitive diagnosis of DKA or HHS must be confirmed through laboratory investigation. However, the clinical presentation can provide helpful information for the preliminary bedside diagnosis [75].

DKA usually occurs in younger, lean patients with type 1 diabetes mellitus and develops within a day or so, whereas HHS is more likely to occur in elderly obese diabetic patients, often those with decreased renal function who do not have access to water; in this cases the HHS may take days or weeks to fully develop [76].

The pathophysiologic consequences of hyperglycemia, hyperketonemia, and insulin deficiency account for many of the classic symptoms and physical findings seen in DKA and HHS. High glucose levels lead to an osmotic diuresis, dehydration, and ultimately hypotension. The high ketone concentrations are responsible for the metabolic acidosis and also cause an osmotic diuresis.

Both DKA and HHS often present with polyuria and polydypsia, although polydypsia may be absent in elderly patients with HHS. In both conditions, abdominal pain with nausea and vomiting can develop owing to acidosis *per se* or to decreased mesenteric perfusion, and can be mistaken for an acute surgical abdomen. Kussmaul–Kien respiration (rapid and deep respiration) with acetone on the breath is typical of DKA but is absent in HHS. Although dehydration occurs in both conditions, it is often more pronounced in HHS. Because DKA and HHS are usually accompanied by hypothermia, a normal or elevated temperature may indicate underlying infection.

Although patients may be alert at the time of presentation, changes in their mental status are common and vary from confusion or disorientation to coma, usually as a result of extreme dehydration with or without prerenal azotemia, hyperglycemia, and hyperosmolarity. In contrast to DKA, focal or generalized seizures and transient hemiplegia may occur.

17.5.2 Laboratory findings

Most patients presenting with DKA have a plasma glucose level of 14 mmol/l or greater. However, most patients with type 1 diabetes mellitus who have such a plasma glucose level do not have ketoacidosis. On the other hand, ketoacidosis may develop in patients with a plasma glucose level below 14 mmol/l. In HHS, hyperglycemia is usually more severe than in DKA, and a plasma glucose level ≥34 mmol/l is arbitrarily one of the diagnostic criteria. Glucose is the main osmole responsible for the hyperosmolar syndrome. The increased serum osmolality can be calculated as follows: (2 × serum Na) + serum glucose, with normal values being 290 (SD 5) mmol/kg water. Blood urea nitrogen is not included in the calculation of effective osmolality because it is freely permeable in and out of the intracellular compartment [52, 77]. By definition, the osmolality must exceed 320 mmol/kg to be diagnostic of HHS. However, it is not uncommon in DKA to have increased osmolality. In DKA the blood pH will be ≤7.30 or less, and in HHS in isolation it will be >7.30. Venous blood can be used to measure pH and bicarbonate levels unless information on oxygen transport is required. It must be remembered that venous blood, without arterial blood gas values, does not permit the identification of mixed acid–base disorders [78]. In DKA, a lower pH will usually be associated with a decrease in bicarbonate to ≤15 mmol/l, although a milder form of DKA may present with a bicarbonate level of 15–18 mmol/l. Less severe DKA is always accompanied by moderate to large amounts of ketones in the blood and urine, while trace amounts may also be found in cases of HHS [79]. Today it is possible to measure blood β-hydroxybutyric acid levels at the bedside, using a reagent strip and a reflectance meter [80].

The majority of patients presenting with DKA and HHS have an elevated leukocyte count, usually in the range 10.0–15.0 × 109/l even in the absence of infection [59], this being attributed to stress and dehydration [74]. Amylase levels are often elevated in patients with DKA, but represent enzyme activity from non-pancreatic tissues such as the parotid gland. Lipase levels will usually be normal. Additional laboratory tests should include blood culture, urinalysis and urine culture, chest radiography, and electrocardiography, as well as measurement of the lactate level if indicated. Because a high fetal mortality rate is associated with ketoacidosis, it is important to eliminate the possibility of pregnancy in women of reproductive age.

17.5.3 Treatment of DKA and HHS

The therapeutic goals for treatment of hyperglycemic crises in diabetes consist of (1) improving the circulatory volume and tissue perfusion, (2) decreasing the serum glucose and plasma osmolality toward normal levels, (3) clearing the serum and urine of ketones at a steady rate, (4) correcting electrolyte imbalances, and (5) identifying and treating precipitating events [81].

The successful of treatment of DKA and HHS depends on adequate correction of dehydration, hyperglycemia, ketoacidosis, and electrolyte deficits [82]. The pathways of management are shown in Figure 17.1.

Any co-morbid precipitating event should be identified and treated appropriately. Both DKA and HHS are medical emergencies, and patients with these conditions must be admitted to hospital.

The treatment of HHS involves frequent and careful monitoring. Although 4–6 l of fluid may be needed during the first 12 h, such rapid replacement may not be feasible in older people, who often exhibit poor cardiac reserve [83]. In most cases, insulin and intravenous fluids can be safely started simultaneously. The exceptions are patients with hypokalemia or hypotension. In such cases, intravenous fluids should be given before insulin to prevent any worsening of hypokalemia or hypotension, which can occur in response to insulin and the resulting intracellular shift of glucose, potassium, and water [84].

17.5.4 Fluid therapy

The objective of an initial fluid therapy is to expand extracellular volume (intravascular and extravascular) and restore renal perfusion. In the absence of major heart problems, it is suggested that treatment start with infusion of isotonic saline (0.9% sodium chloride) at a rate of 15–20 ml/kg h during the first hour (1–1.5 l in the average adult) so as to rapidly expand the extracellular space. The subsequent choice of fluid replacement depends on the state of hydration, electrolyte levels, and urinary output. In general, this may be an infusion of 0.45% sodium chloride at a rate of 4–14 ml/kg/h if the serum sodium level is normal or elevated. The administration of hypotonic saline leads to gradual replacement of the intracellular and extracellular compartments. As soon as renal function is assured, potassium must be added to every liter of fluid. When the plasma glucose level reaches 12–14 mmol/l, each liter of fluid should contain 5% dextrose. Fluid

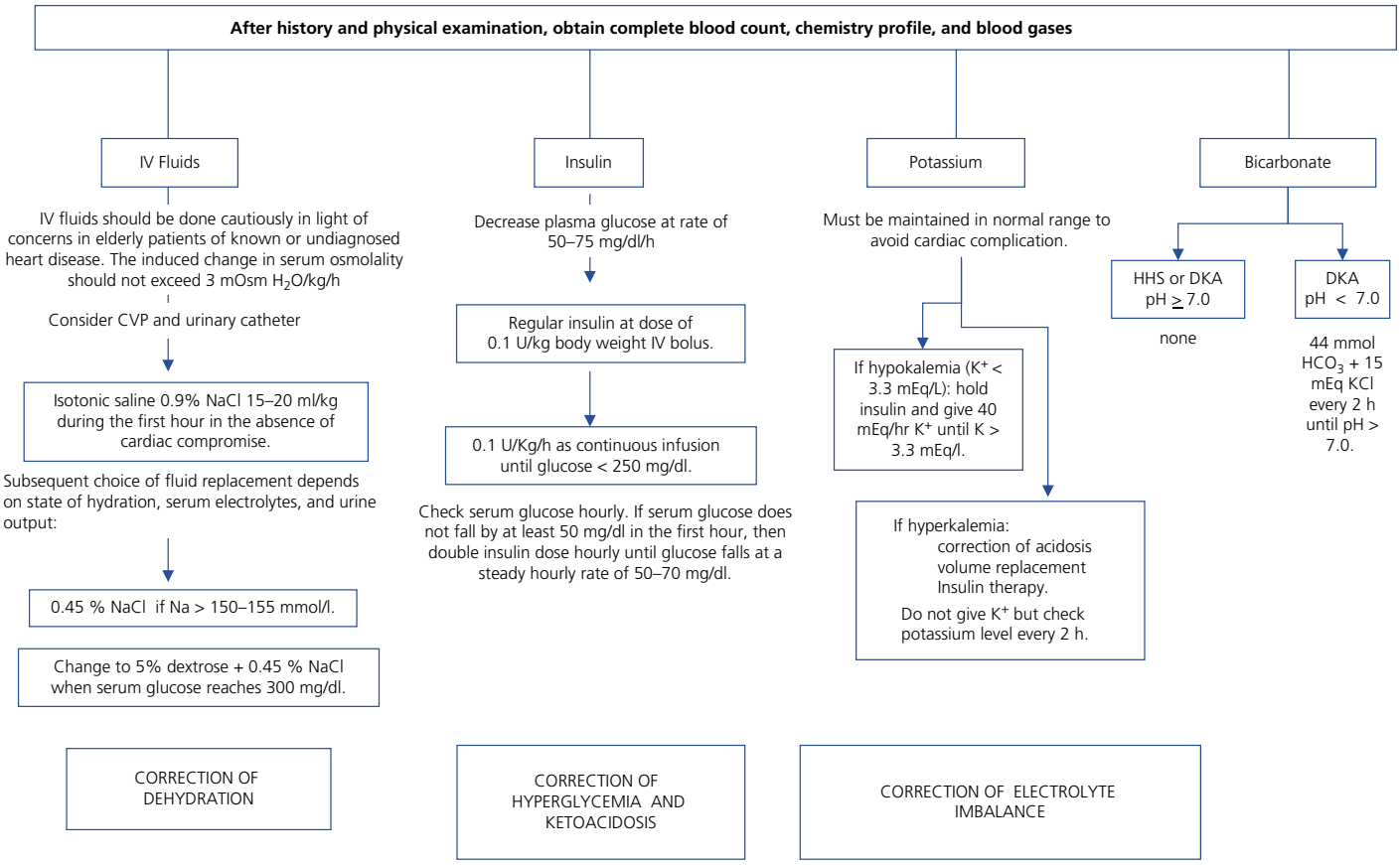

Figure 17.1 Management of patients with DKA and HHS.

replacement should correct the estimated water deficit over the first 24 h. It is important that the change in osmolality not exceed 3 mOsmol/kg/h [52, 53, 72, 85, 86].

In patients with kidney and heart problems, their cardiac, renal, and mental statuses must be assessed frequently, with regular serum osmolality monitoring during rehydration to avoid iatrogenic water overload [52, 53, 72, 85, 86].

Caution is indicated in the elderly patients with heart failure or renal insufficiency in order to avoid fluid overload. Along with frequent clinical and laboratory assessment, bladder catherization and the monitoring of central venous pressure or pulmonary capillary wedge pressure may be warranted to assess fluid status more accurately.

17.5.5 Insulin therapy

There is general consensus that, in cases of DKA and HHS, regular insulin should be administered by means of continuous intravenous infusion in small doses through an infusion pump [55, 66, 85, 87]. Such low-dose insulin therapy provides insulin concentrations that are more physiologic and produce a more gradual and steady fall in plasma glucose levels [88, 89]; the risk of hypoglycemia and hypokalemia is also decreased [55]. The available data do not support the subcutaneous or intramuscular route for insulin administration [51]. Although most proposed protocols suggest that a loading dose of insulin should be given at the initiation of insulin therapy, there are no data to support any advantage for such a recommendation [55, 89].

As soon as hypokalemia (potassium concentration < 3.3 mmol/l) has been excluded, continuous infusion of regular insulin can be started at a dose of 0.1 U/kg/h, which should produce a gradual decrease in the plasma glucose level of 3–4 mmol/l/h [88]. When the plasma glucose level reaches 12–14 mmol/l, the insulin infusion rate may be decreased by 50% as the 5% dextrose is added. Thereafter, the insulin infusion dose must be adjusted to maintain the plasma glucose values until the acidosis in DKA or the clouded consciousness and hyperosmolality in HHS have been resolved.

When the ketoacidosis in DKA has been corrected (plasma glucose level < 11.0 mmol/l, serum bicarbonate level ≥18 mmol/l, venous pH > 7.3, and anion gap < 12 mmol/l), the clouded consciousness and hyperosmolality in HHS have resolved, and patients are able to take fluids orally, a multidose insulin regimen may be initiated based on the patient's treatment before DKA or HHS developed.

Recent clinical studies have demonstrated the potency and cost-effectiveness of subcutaneous rapid-acting insulin analogues (lispro or aspart) in the management of patients with uncomplicated mild to moderate DKA [90, 91]. The patients received subcutaneous rapid-acting insulin doses of 0.2 U/kg initially, followed by 0.1 U/kg every 1 h or an initial dose of 0.3 U/kg followed by 0.2 U/kg every 2 h until blood glucose is <250 mg/dl. The insulin dose was then decreased by half to 0.05 or 0.1 U/kg, respectively, and administered every 1 or 2 h until resolution of DKA. No differences in the duration of hospital stay, total amount of insulin needed for resolution of hyperglycemia or ketoacidosis, or in the incidence of hypoglycemia among treatment groups were found [90, 91]. The use of insulin analogues allowed treatment of DKA in general wards or the emergency department and so reduced cost of hospitalization by 30% without any significant changes in hypoglycemic events [91]. It is important note here that the use of fast-acting insulin analogues is not recommended for patients with severe DKA or HHS, as no studies have been conducted to support their use. Again these agents may not be effective in patients with severe fluid depletion as they are given subcutaneously.

17.5.6 Potassium therapy

The treatment of DKA and HHS with rehydration and insulin is typically associated with a rapid decline in the plasma potassium concentration, particularly during the first few hours of therapy [71–74]. This rapid decrease is due to several factors, the most significant being the insulin-mediated re-entry of potassium into the intracellular compartment. Other factors are extracellular fluid volume expansion, correction of acidosis and continued potassium loss owing to osmotic diuresis, and ketonuria. Despite major potassium depletion in the whole body, mild to moderate hyperkalemia is not uncommon in patients in hyperglycemic decompensation. Because treatment will rapidly induce decreased serum potassium concentrations, potassium replacement must be initiated as soon as levels fall below 5.0 mmol/l, assuming urine output is adequate. It is recommended that 20–30 mmol of potassium be added to each liter of infusion fluid to maintain the serum potassium

concentration between 4 and 5 mmol/l [82]. If the serum potassium level is less than 3.3 mmol/l, then potassium replacement therapy should be started immediately with fluid therapy, and the initiation of insulin therapy should be delayed until the potassium concentration is restored to above 3.3 mmol/l to avoid arrhythmia, cardiac arrest, and respiratory muscle weakness [82].

Initially, the serum potassium level should be measured every 1–2 h because the most rapid change occurs during the first 5 h of treatment. Subsequently, it should be measured every 4–6 h, as indicated clinically.

17.5.7 Bicarbonate and phosphate therapy

17.5.7.1 Bicarbonate therapy

The use of bicarbonate in the treatment of DKA remains controversial [92]. Most current reviews do not recommend the routine use of alkali therapy in DKA because the condition tends to correct with insulin therapy. Insulin administration inhibits ongoing lipolysis and ketoacid production, and promotes ketoanion metabolism. Because protons are consumed during ketoanion metabolism, bicarbonate is regenerated, leading to partial correction of metabolic acidosis. The rationale for bicarbonate therapy is (the theoretical) assumption that severe acidosis could contribute to organ malfunction, such as of the liver, heart, and brain. However, there are few prospective randomized studies of the use of bicarbonate in DKA.

Studies of patients with a blood pH of 6.9 or higher have found no evidence that bicarbonate is beneficial [60], and some studies have even suggested that bicarbonate therapy might be harmful for these patients [61–63]. Because no studies have been conducted on patients with a blood pH below 6.9, the administration of bicarbonate as an isotonic solution is recommended. However, it should be noted that, as bicarbonate therapy lowers potassium levels, these will needs to be monitored very carefully [93].

17.5.7.2 Phosphate therapy

The beneficial effect of phosphate therapy is purely theoretical. It would be expected to prevent potential complications associated with hypophosphatemia, such as respiratory depression, skeletal muscle weakness, hemolytic anemia, and cardiac dysfunction. Furthermore, the majority of controlled randomized trials have been unable to demonstrate any clinical benefit of routine phosphate therapy [55] but still recommend that one-third of potassium replacement be given as potassium phosphate. No studies have been conducted on the use of phosphate therapy for HHS.

17.5.8 Clinical and laboratory follow-up

Vital signs should be monitored at 30-min intervals, hourly for the next 4 h and then every 2–4 h until resolution of the condition. An accurate record of hourly urine output is necessary to monitor kidney function. On admission, a comprehensive profile will include at least arterial or venous blood gas values, levels of plasma glucose, electrolytes, blood urea nitrogen and creatinine, ketone levels in serum or urine (or both), and serum osmolality. Capillary blood glucose levels should be monitored hourly to allow any adjustment of the insulin infusion dose. Electrolyte levels should be measured every 1–2 h initially, and every 4 h thereafter. The measurement of venous pH can replace that of arterial pH and should be undertaken every 4 h until the DKA has been corrected.

17.5.9 Treatment-related complications

Common complications of DKA include hypoglycemia, hypokalemia, and recurrent hyperglycemia, all of which may be minimized by careful monitoring. Hyperchloremia is a common, but transient finding that usually requires no special treatment.

Cerebral edema is a rare but important complication of DKA. Although it can affect adults, it is more common in young patients. The early signs of cerebral edema include headache and confusion, while lethargy, papilledema, hypertension, hyperpyrexia, and diabetes insipidus may also occur. Patients typically improve mentally with initial treatment of DKA, but then suddenly worsen. Multiple factors in the treatment of DKA and HHS may contribute to the cerebral edema, including (i) the idiogenic osmoles, which cannot be dissipated rapidly during rehydration, thus creating a gradient and a shift of water into the cells [55], (ii) insulin therapy *per se*, which may promote the entry of osmotically active particles into the intracellular space, and (iii) the rapid replacement of sodium deficits [53, 73].

To reduce the risk of cerebral edema, it is recommended that physicians correct sodium and water deficits gradually and avoid the rapid decline in plasma glucose concentration [51, 82].

17.5.10 Adult respiratory distress syndrome

Adult respiratory distress syndrome, or non-cardiogenic pulmonary edema, is a potentially fatal complication of DKA that fortunately occurs rarely [55]. The partial pressure of oxygen, which is normal on admission, decreases progressively during treatment to unexpectedly low levels. This change is believed to be due to increased water in the lungs and reduced lung compliance. These changes may be similar to those occurring in brain cells leading to cerebral edema, which suggests that it is a common biological phenomenon in tissues [55].

17.5.11 Hyperchloremic metabolic acidosis

This phenomenon is not uncommon during the treatment of DKA [69]. A major mechanism is the loss of substrates (ketoanions) in the urine that are necessary for bicarbonate regeneration [69, 94]. Other mechanisms include (i) intravenous fluids containing chloride concentrations exceeding that of plasma [94, 95], (ii) volume expansion with bicarbonate-free fluids [94, 95], and (iii) intracellular shift of sodium bicarbonate during correction of DKA [96]. This acidosis usually has no adverse effect and is corrected spontaneously in the subsequent 24–48 h through enhanced renal acid excretion [94–97].

17.5.12 Vascular thrombosis

Many features of DKA and HHS predispose the patient to thrombosis, including dehydration and contracted vascular volume, a low cardiac output, increased blood viscosity, and the frequent presence of underlying atherosclerosis [66, 67]. In addition, a number of hemostatic changes favor thrombosis [98]. This complication is more likely to happen when osmolality is very high. Low-dose or low-molecular-weight heparin therapy should be considered for prophylaxis in patients at high risk of thrombosis. However, there are no data demonstrating its safety or efficacy.

17.5.13 Hypoglycemia and hypokalemia

These complications are less common with current low-dose insulin therapy [55, 87, 88]. The potassium deficit should be adequately corrected and 5% dextrose should be added to infusion fluids as soon as the plasma glucose level drops below 12–14 mmol/l.

17.6 Conclusion

Much remains to be done to lower the incidence of DKA and HHS and to improve the outcome of patients with these conditions. Although it has been suggested that the rate of death associated with these complications is decreasing, the rate is still excessive [99].

The various factors that can precipitate hyperglycemic decompensation in patients with diabetes should alert the physician to early diagnosis and prompt therapy.

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CHAPTER 18
Nutrition management

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KEY MESSAGES

- Older people are at high risk of under- or malnutrition. These conditions impact on most other domains of functioning.
- Some obese older people with diabetes have various degrees of under/malnutrition.
- Comprehensive nutritional assessments should be undertaken regularly and on admission to hospital.
- The interdisciplinary healthcare team should be involved in nutrition assessment.
- Oral supplements can increase energy and nutrient intake. They may be needed in routine care and during palliative care.
- Nutrition requirements should be tailored for the individual and developed with the individual considering their food beliefs, the social and personal meaning of food, preferences, cultural traditions, self-care capability, economic factors, and the support available to help the individual manage their nutrition plan.
- The nutrition plan should be considered in light of the medicine regimen: most glucose-lowering medicines need to be taken with food, some medicines should be not taken with food, and food–medicine interactions can occur.

18.1 Introduction

Diabetes is a global epidemic, affecting 8.6 million adults aged over 65 years [1], approximately one in 50 people over 65. The prevalence rises to 33.6% when impaired fasting glucose (IFG) is included. From age 60, the lifetime risk of developing diabetes is high: 22.4% for women and 18.9% for men [1]. The prevalence is increasing despite knowledge that healthy eating and regular exercise can prevent diabetes (Chapter 4). In 2011, 368 million people had diabetes world-wide and the proportion is predicted to increase to 552 million by 2030, especially in low- and middle-income families [2].

It is important to recognize the heterogeneity in the spectrum of health among older people, so that health interventions, including nutrition, can be personalized to suit the individual's situation. The nutrition plan must be appropriate for the individual's functional status, their diabetes complications and other co-morbidities, social situation, medicine regimen, and available support when help is required. As a person's life expectancy may be shorter than the time needed to benefit from an intervention, it is important to prioritize treatment strategies. Managing one or more co-morbidities and palliative and end-of-life care might take precedence over managing diabetes *per se* [3].

Several physiological changes associated with aging predispose older people to diabetes; moreover, once diabetes is diagnosed, insulin resistance is invariably present and may be associated with obesity [4]. In contrast, there is a high prevalence of malnutrition in older people, especially those living in aged-care facilities and in hospital settings [4]. Malnutrition occurs in 25–30% of older people in hospital and a further 46–61% are at risk of malnutrition [5]. The impact of malnutrition

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could be more deleterious if nutrition counselling is inadequate and not personalized.

Good nutrition is essential to health and wellbeing, and, along with regular physical activity, is the basis of diabetes management as well as managing diabetes complications such as cardiovascular disease (CVD), which accounts for75% of deaths in people with chronic disease. However, it is important to recognize that adherence to nutrition recommendations is low when providing nutrition counseling. Over 49% of adults do not eat enough fruit, 92% do not eat enough vegetables, and many are inactive [6]. In addition, many older people consume more than the recommended alcohol intake. A systematic review (n = 9445) suggests that strategies that improve adherence include nutrition counseling, education videos, incentives, nutrition tools such as carbohydrate calculators, and that using a combination of interventions is more likely to succeed [7].

18.2 Basis of nutrition support

Peake [8] suggested the following basic questions could be considered when designing nutrition program for people with hyperglycemia or diabetes:

- What is the person's nutrition status?
- Can the nutrition requirements be met orally?
- Is artificial nutrition indicated?
- Are there any gastrointestinal disorders?
- Should enteral or parenteral feeding be used?
- What formula will suit the individual's needs?
- What is an acceptable [safe] blood glucose range for the individual?
- What glucose-lowering medicine types and regimen will be safe and effective, and how will the nutrition plan relate to the medicine regimen?

18.3 Nutrition and normal aging

18.3.1 Changes in appetite and food intake with increasing age

There is an association between impaired sense of smell and reduced interest in and intake of food. The senses of taste and smell deteriorate with age, by 60–80% in some people. Therefore, people tend to have little appetite and eat less as they grow older. Healthy older people often do not feel hungry, consume smaller meals, eat more slowly, eat fewer snacks between meals, and become satiated more rapidly after eating a standard meal than do younger people [9]. However, as the energy intake is often less than the reduction in energy expenditure; consequently older people tend to lose weight, which is referred to as "the anorexia of aging". In aging individuals, as a greater proportion of body fat is intrahepatic, intramuscular, and intra-abdominal compared with subcutaneous fat in younger people, it is uncertain whether these fat deposits are affected in the same way during the anorexic process and cause weight loss but we know that these changes are associated with increased insulin resistance and, therefore, are likely to be associated with adverse metabolic outcomes and cardiovascular risk [10].

Changes in gut motility occur with age and gastric emptying is slower in older people, but does not usually lead to the problems commonly associated with gastric autonomic neuropathy. However, gastroparesis does occur and must be considered when assessing nutritional status. The capacity of the stomach to distend to accommodate the influx of food also reduces and may induce an earlier satiety and the individual might reduce their food intake. Gastrointestinal changes only play a minor role in nutrition status compared to the many other reasons for malnutrition in older people.

18.3.2 Changes in body weight with increasing age

Several large cross-sectional studies show that both body weight and body mass index (BMI) increase throughout adult life until about age 50–60 years, after which they decline. A few older people have a marked weight change over time. In one study [11], 17% of home-dwelling people in the USA aged >65 years lost ≥5% of their initial bodyweight over 3 years, whereas 13% gained 5% or more. A BMI range between 24 and 29 kg/m^2 is appropriate for older people [11], especially for individuals aged over 70 years, because a higher BMI range is associated with lower mortality rates [12]. Morley suggested that weight reduction is only a consideration in older people who are 20% above their desirable body weight, where a BMI of 29 kg/m^2 may be a safer target for older people to achieve [13]. A weight loss between 5% and 10% from initial body weight improves blood pressure, glycemic control, and lipid profiles.

It is also important to consider the mechanical effects of obesity on the individual's functional capacity, ability to exercise, and ability to perform important activities of daily living such as foot care and hygiene.

18.3.3 Changes in body composition with increasing age

There is a progressive increase in fat and decrease in fat-free mass as people age due to loss of skeletal muscle; which may be up to 3 kg of lean body mass per decade after the age of 50. Consequently, at any given weight, older people have more body fat than younger adults but the fat is located in different places. Age-related increase in body fat is multifactorial in origin. Less physical activity is a major contributing factor along with reduced growth hormone secretion, declining sex hormone action, reduced resting metabolic rate, and the thermic effect of food.

18.3.4 The anorexia–sarcopenia–sachexia triad in older people

Malnutrition in older people appears to be caused by inadequate food intake that leads to anorexia and, through inflammatory processes, induces cachexia. Although anorexia, sarcopenia, and cachexia have some common features, anorexia mainly refers to low calorie intake that leads to loss of body fat mass. Anorexia is distinct from sarcopenia, where primarily lean body mass (muscles) is lost, which compromises functionality (Table 18.1). Cachexia leads to loss of fat and muscle mass, and is commonly observed in people with advanced stage cancer [14]. The resultant weight loss and associated under-nutrition can contribute to adverse outcomes such as frailty and falls, especially after age 60.

Table 18.1 Overview of the pathophysiology of malnutrition.

Triad of malnutrition	
Anorexia/ under-nutrition	Deficient caloric intake (loss of fat mass)
Sarcopenia	Protein-deficient diet and lack of physical exercise (loss of muscle mass)
Cachexia	Catabolic state Inflammatory parameters increased (TNF-α, IL-1, IL-6) (loss of both fat and muscle stores)

Excessive loss of lean body tissue can lead to sarcopenia, which is defined as muscle mass more than two standard deviations below the sex-specific young-normal mean, and is present in 6–15% of people aged 65 years [15]. Unlike the loss of fat tissue, loss of skeletal muscle is associated with metabolic, physiological, and functional impairments and disability, including increased falls and increased risk of protein-energy malnutrition. The National Health And Nutrition Examination Survey (NHANES) III study found older people who had marked sarcopenia were between 3.3-fold (women) and 4.7-fold (men) more likely to have a physical disability than those with appropriate skeletal muscle mass [15].

Aging *per se* appears to be partly triggered by inflammatory processes that increase the oxidative stress and its adverse effects over the life-span. Significantly, malnutrition can be present in lean and obese older people because both situations are caused by an inflammatory process. Lean people are malnourished due to diminished food intake that leads to anorexia and posterior cachexia. Obese people are malnourished because obesity can be associated with increased fat body mass and high BMI as well as with low lean body mass and sarcopenia. Lean body mass has a very low metabolic rate and responds poorly to low calorie diets, which can exacerbate malnutrition. Therefore, both malnourished and obese older people with diabetes reflect two types of inflammatory states but are metabolically different and require different nutrition approaches.

18.4 Under- and malnutrition in older people

18.4.1 Prevalence

Under-nutrition refers to a state of energy, protein, and other specific nutrient deficiencies that leads to measurable changes in body function and compromises recovery from illness. Under-nutrition can be reversed with nutrition support [7, 8]. It contributes to functional decline, increased hospital admissions and longer length of stay, compromises the individual's ability to live independently, and increases falls risk and mortality [7, 16]. It also contributes to increased bone loss, hip fracture, and pressure ulcers when BMI is < 22 kg/m^2 and is an independent predictor of new disabilities [16], pain and suffering.

Protein-energy malnutrition is common in older people: up to 15% of community-dwelling and housebound older people, between 23% and 62% of hospitalized older people, and up to 85% of residents in aged homes in developed countries are malnourished [8, 15]. Protein-energy malnutrition is associated with impaired muscle function, reduced bone mass, immune dysfunction, anemia, reduced cognitive function, poor wound healing, delayed recovery from surgery, and, ultimately, increased morbidity and mortality.

Epidemiological studies show that protein-energy malnutrition is a strong independent predictor of mortality in elderly people, regardless of whether they live in the community or in an aged-care home, are in hospital, or were discharged from hospital during the past 1–2 years [17–19]. Mortality is increased in the presence of other diabetes-related complications and co-morbidities such as renal failure, cardiac failure, and cerebrovascular disease. Two of the most common markers of under-nutrition and risk of morbidity and mortality are low body weight and weight loss.

Estimating the prevalence of malnutrition in older people depends on the tools used to evaluate nutritional status and on the sampling population. Previously, anthropometry, reports of recent weight loss, biochemical markers, and the Mini Nutritional Assessment or other composite nutritional evaluation tools were used alone or in combination. Various studies reported an association between mortality and nutritional status assessed by BMI, weight loss, serum albumin or food intake. However, it is important to consider other potential predictors of adverse outcomes, such as illness severity, co-morbidity and functional status, especially in older people with diabetes.

In hospital, both age and serum albumin have significant effects on mortality. One study of hospitalized people showed the lower the serum albumin on admission and the older the patient, the higher the risk of death [20]. Likewise, 21% of 497 people aged ≥65 years had an average daily in-hospital nutrient intake <50% of their calculated maintenance energy requirements and the low nutrient intake group had a higher rate of in-hospital mortality (RR = 8.0; 95% CI 2.8–22.6) and 90-day mortality (RR = 2.9; 95% CI 1.4–6.1) [21].

These findings suggest prescribing low-energy and/or low-fat diets for older peoples with diabetes in hospital can markedly reduce the average daily nutrient intake of maintenance energy requirements and compromise nutritional status. Weight loss and malnutrition have also been associated with other adverse outcomes in older people, such as longer length of stay in hospital, influencing the discharge location, time to readmission, infections, gait disorders, falls and fractures, and poor wound healing. Consequently, it is essential to undertake a comprehensive nutrition assessment of all older people when they are admitted to hospital or aged-care homes. The interdisciplinary team should be involved.

18.4.2 Low body weight in older people

Body weight tends to decrease after age 60, when loss of ≥5% of body weight is common in older people. The relationship between mortality and body weight is a J-shaped curve, where mortality increases at low and high BMI values. BMIs associated with the greatest life expectancy for young adults range between 20 and 25 kg/m^2. The BMI associated with maximum life expectancy increases with age. The lower end of the range increases to about 22–23 kg/m^2 while the upper end increases to 27–28 kg/m^2 for people aged >65 years. BMI below 22–23 kg/m^2 is associated with a steady increase in risk of death, mainly at BMI values <18.5 kg/m^2 in women and 20.5 kg/m^2 in men [22].

Mortality doubled in the most underweight (BMI <18 kg/m^2) in a cohort of 8428 hospitalized patients aged 20–40 years, compared to groups with BMIs between 20 and 40 kg/m^2 in patients aged 70–79 years. Mortality tripled when BMI was <18 kg/m^2 compared groups with BMIs between 32 and 40 kg/m^2 [23]. These findings suggest being very underweight increases mortality risk as people age (Figure 18.1).

18.4.3 Causes of under-nutrition in older people

Healthy aging is associated with a decline in energy (food) intake, physiological "anorexia of aging", and changes in homeostatic mechanisms that restore food intake in response to anorectic insults in younger people. Roberts *et al.* [24] demonstrated these changes by underfeeding young and older men by approximately 750 kcal per day for 21 days: both groups of men lost weight. When the men were allowed to eat *ad libitum* after under-feeding, young men ate more than at baseline and quickly returned to normal weight. In contrast, the older men did not compensate, returned only to their baseline intake, and did not regain the weight they lost.

Many factors can prevent older people from meeting their nutrition needs, including socioeconomic factors

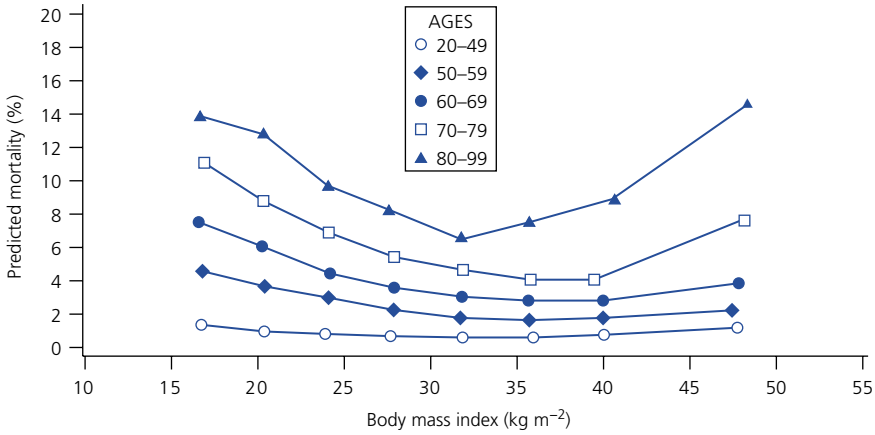

Figure 18.1 Association between BMI and mortality as a function of age in 8428 hospitalized patients. Reproduced from [32].

such as income, knowledge, transportation, literacy and numeracy isolation, and limited social support such as not being married [25]. However, social and emotional factors concerning food also influence nutritional status and are less obvious without a careful comprehensive personal assessment and actively listening to the individual and their families. Eating behaviors are primarily determined by cultural food traditions and social and psychological factors [26].

Older people face many challenging life transitions, such as divorce/widowhood, moving out of home into an aged-care facility, and loss of mobility and independence, which influence mood and eating behaviors. Companionship and sharing meals enhances nutrition [27]. The memories and meaning associated with food become more important as people age and especially in aged-care homes. Respecting food preferences is important yet might not be achievable in aged-care homes [28]. However, it is possible to ensure the older person can reach their food, assist them to eat if necessary, and ensure mealtimes are protected and pleasant.

Eating disorders such as bulimia and anorexia nervosa are rare in older people, but they do occur, although there is little information about the topic [29]. The prevalence appears to be low, for example 3.8% of community-dwelling older Canadian women aged 60–70 years (n = 475) and 11–19% of under-nourished older males attending outpatient clinics. Underlying causes of eating disorders include changing physical appearance (usual age-related changes), changes in familial relationships, and the need to be in control and to seek attention.

Some older people who present with an eating disorder had an eating disorder when they were young and never recovered, some have a remitting, relapsing eating disorder, and some develop an eating disorder after age 50, often following a stressful event such as admission to an aged-care home or the death of a family member or beloved pet [29]. Older people may present with a range of symptoms, including excessive exercise, vomiting and/or laxative use, rigid/restrictive eating, preoccupation with body image and plastic surgery, and co-morbid psychiatric conditions.

Management usually consists of behavioral and pharmacological therapies but they must be tailored to the individual. Some factors unique to older people that need to be explored include:

- family influence: role in supporting the older person and ability to advocate for the older person if they are unable to advocate for themselves
- co-morbidities that contribute to weight loss
- medication: some medicines reduce appetite and some stimulate it
- sensory loss: vision, hearing and touch
- cognitive changes: cognitive behavioral therapies might be inappropriate [29].

18.4.4 Pathologic anorexia and under-nutrition in older people

Protein-energy malnutrition is likely to develop when other "pathological" factors are present, which is common with increasing age. Identifying underlying pathological and psychological factors is important

because many respond to treatment. Older people are more likely to live alone than young adults and social isolation and loneliness are associated with reduced appetite and energy intake in older people, who consume substantially more food during a meal when they eat in the company of friends [30].

Depression is a common problem in older people. It occurs in 2–10% of community-dwelling older people, in a significant majority of older people in aged-care homes, especially if they have cognitive impairment [24, 27], and often in hospital. Depression is more likely to manifest as reduced appetite and weight loss in older people and is an important cause of weight loss and under-nutrition. Depression is an underlying cause of under-nutrition in 30–36% of older people attending outpatient clinics and residents in aged-care homes. Under-nutrition can worsen depression, particularly if it leads to folate deficiency.

Treating depression can lead to appropriate weight gain and improve other nutritional indices [31] as well as functioning, wellbeing and quality of life. Depression is discussed in Chapter 33. Some antipsychotic medicines contribute to weight gain and some might be contraindicated or need to be used with caution in older people (Chapter 21).

Oral health problems, dental and gum disease, and ill-fitting dentures can affect the type and quantity of food the individual eats [7]. Difficulty chewing, biting, and swallowing food are common among residents in aged-care home, and older people who wear dentures are more likely to have inadequate protein intake [32]. Polypharmacy is common in older people (Chapter 21) and increases the risk of medicine adverse events and interactions that can contribute to or cause anorexia. Some medicines, such as antipsychotics, lead to weight gain and some diuretics cause excessive urination, which can contribute to dehydration and electrolyte changes [5].

18.5 Over-nutrition and obesity in older people

Obesity is defined as excess body weight and is a diagnosis in its own right [33]. It is caused by a number of interrelated factors, including genetic, hormonal and environmental factors such as high-saturated fat, energy-dense diet, little physical activity, and occupational sitting.

18.5.1 Prevalence

Many older people in developed countries are overweight using standard BMI criteria, and obesity is increasing globally. In 2000, 58% of Americans aged ≥65 years had a BMI of ≥25 kg/m^2 or more and the prevalence of obesity (BMI > 30) in people in the USA aged >70 years increased by over one-third between 1991 and 2000, from 11.4% to 15.5% [34]. Similar trends are occurring globally [2].

The increase in the relative risk of death associated with obesity is generally lower in older people than in young adults. For example a review of 13 studies in which non-hospitalized people aged >65 years who were followed for at least 3 years only showed an association between mortality and high BMI in a few cases, and then only at BMIs > 27–28.5 kg/m^2 [34]. There was little or no increase in mortality at any BMI in people aged >75 years. Where an optimum BMI could be identified, it usually ranged between of 27 and30 kg/m^2.

Common causes of increased mortality include diabetes, which is an underlying cause of most other common causes of death, hypertension, sleep apnea, CVD, and some cancers, including breast, uterus, colon, and prostate. Functional capacity and mobility are reduced significantly in obese older people, who have a lower quality of life, greater limitations of physical function, and are more likely to be housebound [35]. Obesity predicts a greater rate of future disability, declining functional status, and increased likelihood of admission to an aged-care home.

A progressive rise in fasting and postprandial plasma insulin concentrations is a characteristic abnormality of glucose metabolism in older people, which suggests aging is an insulin-resistant state. The liver maintains normal glucose levels postprandially and during fasting, but with increasing age more insulin is required to regulate hepatic glucose production and prevent hyperglycemia [36]. Beta cells do not secret sufficient insulin in the face of hepatic and peripheral insulin resistance, which leads to hyperglycemia, pre-diabetes, and eventually type 2 diabetes. Moreover, hyperglycemia reduces muscle and liver sensitivity to insulin and impairs beta-cell function, a phenomenon referred to as “glucose toxicity.”

Insulin resistance and hyperinsulinemia are associated with increases in total and visceral fat mass, which is typical of aging (see Chapter 17). Insulin resistance is an independent risk factor for of CVD and is associated

with hypertension, dyslipidemia and dysfibrinolysis. These abnormalities constitute pre-diabetes, previously known as the metabolic syndrome, insulin-resistance syndrome, and syndrome X. Pre-diabetes is a major risk factor for CVD, cancer, and all-cause mortality, and reduces life expectancy. Pre-diabetes must be considered when older people are admitted to hospital and to aged-care homes to ensure diabetes is diagnosed early and appropriately treated, and to reduce the associated adverse events such as hyperosmolar states, which are more common in undiagnosed older people (Chapter 19).

There is a strong association between obesity and insulin resistance. Insulin sensitivity improves with weight loss, which suggests there is a causal relationship between obesity and insulin resistance. Changes in body composition during aging contribute to insulin resistance and consequently to the increased prevalence of type 2 diabetes in older people. These age-related pathophysiological changes need to be considered when designing care and education plans, and prescribing medicines for older people with diabetes. Most management strategies are designed to improve carbohydrate homeostasis by weight reduction to improve insulin sensitivity and reduce the deleterious effects of glucose toxicity.

However, as indicated, weight loss might be contraindicated in older people and contribute to adverse health outcomes. Normal weight older people are more likely to die from any cause than heavier people with type 2 diabetes after adjusting for demographic factors, smoking, and CVD risk [37].

Abdominal fat is not inert. It stores triglycerides as energy substrates and produces a number of signaling molecules (adipokines) that play a major role in hormone metabolism and contribute to overall wellbeing. Changes in adipokines associated with obesity include increases in:

- TNF-alpha, which leads to reduced insulin signaling and endothelial vasodilation
- interleukin 6, which increases CRP and insulin resistance, and damages the endothelium
- PAI-1, which induces a prothrombic state
- leptin, which regulates appetite, energy expenditure, and insulin sensitivity
- angiotensin, which plays a role in hypertension.

Adiponectin is usually reduced in obesity. It plays a key role in insulin sensitivity in tissues, is anti-inflammatory, and reduces atherogenesis. These adiponectin functions are compromised in obesity. In addition ghrelin in the stomach mediates hunger but production is compromised in obesity. The endocannabinoid neuroregulatory system also plays a role by influencing the activity of other neurotransmitters and hormone secretion.

18.5.2 Should overweight older people be advised to lose weight?

The adverse effects of obesity, reduced life expectancy at high BMIs up to the age of at least 70 years, and improvements in function are associated with weight loss need to be balanced against the detrimental effects of weight loss on muscle mass and bone density, and the all-cause mortality in overweight older people. The available evidence suggests it is safe to recommend weight loss to overweight older people who have obesity-related morbidities, particularly reduced mobility and function. The focus should be on managing disabilities such as sleep apnea and functional deficits, and optimizing function, rather than weight loss in most older people.

18.6 Nutrition assessment

Before commencing nutritional support, the indications, aims/objectives, and ideal administration route of nutrition support if needed must be determined. Such decisions need to be based on a comprehensive nutrition assessment that might involve the interdisciplinary team and the family, and should actively involve the individual where possible. The clinical features of the condition being treated and life expectancy are important considerations. Older people with hyperglycemia are a heterogeneous group. It is vital to identify the etiology of the individual's hyperglycemia in order to tailor their care and nutrition goals.

The stress response to trauma/illness commonly exacerbates hyperglycemia in people with pre-existing diabetes, and often causes significant hyperglycemia in previously euglycemic patients due to increased production of the counter-regulatory hormones glucagon, cortisol, growth hormone, and adrenaline in response to stress. The stress or counter-regulatory response increases hepatic glucose production, reduces peripheral glucose uptake, and increases insulin resistance. However, it is important to consider the individual's

recent blood glucose pattern when assessing their need for nutrition support because poor glycemic control can compromise their overall nutrition status.

Detailed discussion of the methods used to diagnose under-nutrition in older people with diabetes is beyond the scope of this chapter: there is no "gold standard." Multiple methods are used. The most important factor is to know the person's diagnosis and use effective, valid screening tools such as the ASPEN guidelines [38]. After screening a more detailed assessment can be undertaken by appropriately qualified staff, including a dietitian. The dietary intervention, including the need for supplements, depends on the finding of the comprehensive assessment and life expectancy. The following information describes the key aspects of nutritional screening and assessment.

All people over age 65 should be screened once a year and weighed at regular intervals, particularly those in aged-care homes or other institutions because they are prone to nutritional deficiencies and frailty. Weight loss >5% is usually a key indicator of nutritional risk, as is BMI < 22 kg/m^2. The latter is particularly likely for BMI < 18.5 kg/m^2 [39].

Low serum albumin, hematocrit, lymphocyte count, and serum folate are commonly associated with increased risk of under-nutrition and poor outcomes [40]. Anthropometric measures are an important part of the nutrition assessment and include the following:

- Weight measurements use height/weight standards suitable to the culture. Weight by itself does not reflect the fact that lean body mass can weigh more than fat or muscular builds at different heights. It is useful to monitor weight over time (serial weights).
- BMI has similar limitations to weighing.
- Waist/hip ratio is measured when the person is standing and is a commonly used measure of abdominal obesity. It can be affected by postprandial state, time of day, depth of inspiration, and the position of the measuring tape. It includes both intra-abdominal and subcutaneous fat but it is not clear how to adjust for subcutaneous fat. Ascites can affect the measurement.
- Arm circumference.
- Skin-fold thickness.

Commonly used nutrition screening tools include the following:

- Mini Nutritional Assessment (MNA) [41].
- Short form of the Mini Nutritional Assessment (MNA-SF [42]). If the score is ≤11 the individual is at risk of malnutrition and the full MNA must be carried out.
- MNA measures correlate well with nutritional intake, anthropometry, laboratory data, functionality, morbidity, length of stay, and mortality [43]. However, the individual needs to be able to cooperate with staff undertaking the assessment so the MNA might not be appropriate for cognitively impaired individuals.
- Nutritional risk screening (NRS) is used when the individual is unable to cooperate with the staff undertaking the assessment. NRS emphasizes the severity of concomitant diseases when screening for nutritional risk. NRS is recommended for people of all ages in hospital [44–46]. If the total NRS score is ≥3, some form of nutritional support should be given. Table 18.2 depicts commonly used nutritional screening methods. NRS can be used initially for some groups of older people who have a high prevalence of malnutrition. For example:
  - frail older people living independently in the community with some support
  - older people with several diabetes-related complications and other co-morbidities
  - residents in aged-care homes
  - people in hospital [38].

Food consumption can be measured using 3-, 5-, or 7-day food diaries (records) or diet recall for the past 24 hours. Food records can be very burdensome for many older people and are not suited to people with cognitive deficits unless they have assistance to record their food intake. Food frequency questionnaires can also be used but have similar limitations. Trained observers in hospitals and aged-care homes can record food consumption, classify food types (carbohydrate, protein, and fat), and estimate the amount of food consumed. Observing and recording food can be intimidating for the individual being observed ("the food police"), is costly, and there can be significant inter-observer variability.

It is essential to obtain an accurate medical history that includes weight pattern over the life span, eating behaviors, and eating disorders. Weight loss should be expressed either in kilograms or as a percentage of the individual's usual weight. The duration of time since the weight loss started should also be explored. The person should be asked about their appetite and any changes in their diet and reasons for the changes. Alcohol and tobacco use can affect health generally, as well as nutritional status, and should be included in the assessment. Any physical signs of malnutrition such as

Table 18.2 Common methods used to undertake nutrition screening.

Technique	Use	Parameters studied
Mini Nutritional Assessment (MNA) [41]	Evaluation of nutritional status, validated in the elderly For use in outpatient setting, community and nursing homes if possible	*Anthropometrics*: weight, height, arm and calf circumferences and weight loss *General assessment*: mobility, lifestyle and medication *Dietary assessment*: food and fluid intake, number of meals, and autonomy of feeding *Subjective assessment*: the patient's perception of their own health and nutrition
Nutrition Risk Index (NRI) [46]	Evaluation of nutritional status in the elderly for all hospital patients without age restriction	A 16-item questionnaire including mechanics of food intake, dietary restrictions, morbid conditions affecting food intake, discomfort associated with outcome of food intake and significant changes in dietary habits
Malnutrition Universal Screening Tool (MUST)	Identifies adults who are malnourished, at risk of malnutrition or obese For use in hospitals, community and other care settings	A five-step screening tool using height and weight, percentage unplanned weight loss, acute disease effect together to obtain overall risk of malnutrition
Subjective Global Assessment (SGA)	Identifies risk of developing nutrition-related complications	*Nutritional history*: previous 6 months' weight loss, pattern of dietary intake, presence of gastrointestinal symptoms, functional capacity *Physical examination*: loss of subcutaneous fat, muscle wasting, loss of fluid
Prognostic Nutritional Index (PNI)	Identifies increased risk of post-surgical complications	Combines anthropometry, delayed-hypersensitivity skin test and plasma protein levels, expressed as a single value

muscle atrophy, loss of subcutaneous fat, and peripheral edema as a consequence of hypoprotinemia should be noted.

Fluid intake should also be explored. Older people often have reduced thirst sensation and might not drink adequate fluids and be at risk of dehydration. Dehydration can be a particular problem in hot countries and during hot periods. The older person might need to be reminded to drink. In hospitals and aged-care homes it is important to place fluids where the person can reach them and to check whether they drink. Fluid intake can be included in a food diary, if it is used.

It is also important to review the medicine regimen. Polypharmacy and individual medicines can affect nutrition status. Some medicines that can affect nutrition status in various ways include:

- antibiotics
- opiates
- SSRI
- theophylline
- L-dopa
- NSAIDs
- anticonvulsants
- chemotherapy
- calcium antagonists.

These medicines don not necessarily need to be stopped but their effect on weight and other safety and prescribing issues needs to be considered as part of a comprehensive nutrition and geriatric assessment (Chapter 21).

Older peoples' functional status is closely related to their nutritional status, therefore it is important to determine the individual's basic and instrumental activities of daily living (ADLs and IADLs) and information about their living conditions and social relationships. Morley's mnemonic MEALS ON WHEELS summarizes a variety of treatable pathological causes of under- and malnutrition [47]. Chronic diseases and medicines increase the risk factors of malnutrition in older people because they affect appetite, food intake, gastrointestinal function, and metabolism (Tables 18.3 and 18.4).

The cut-off point below which malnutrition is highly probable in adults aged <65 years is 18.5 kg/m^2, but, for

Table 18.3 Mnemonic 'Meals on Wheels' [11].

Medications (e.g., digoxin, theophylline, fluoxetine)
Emotional causes (depression)
Alcoholism
Late-life paranoia
Swallowing problems (dysphagia)
Oral problems
Nosocomial infections (TB, *Clostridium difficile, Helicobacter pylori*)
Wandering (dementia)
Hyperthyroidism, hyperparathyroidism, hypoadrenalism
Enteral problems (malabsorption)
Eating problems (inability to self-feed)
Low-salt, low-fat diet
Shopping and social problems

Table 18.4 Chronic diseases and medicines that contribute to malnutrition in older people (social factors such as ability to shop, social isolation, food beliefs and experiences, financial status, nutrition knowledge also have a role).

Chronic diseases	Medicines
Chronic cardiac failure	ACE inhibitors
Chronic pulmonary diseases	Analgesics
Cancer	Antacids
Chronic infectious diseases	Anti-arrhythmics
Gastrointestinal diseases	Antibiotics
Diabetes	Anti-epileptics
Severe osteoarthritis	Antidepressants
Hypothyroidism	β-blocking agents
Hyperthyroidism	Calcium channel-blocking agents
Cerebral ischemia	Digoxin/digitoxin
Intracerebral bleeding	H_2-receptor antagonists
Pressure ulcers	Laxatives
Parkinson's disease	NSAIDs
Dementia	Glucose-lowering medicines
Depression	Potassium
Cognitive impairment	Corticosteroids
Renal disease	
Delirium	
Oral health problems	

prognostic reasons, 20–22 kg/m² is usually accepted as the cut-off point in older people [11]. Older people should not be labeled malnourished on the basis of one abnormal anthropometric or pathological value: all available information should be taken into account (Table 18.5).

Table 18.5 Essential criteria for diagnosing malnutrition in older people.

Weight loss (expressed in kg or percentage of former/usual weight)
Oral intake (simple documentation, e.g. using the eye-ball method)
Body mass index <22 kg/m² (showing an acceptable association with body fat stores)
Calf circumference <31 cm (showing a good correlation with muscle mass and functional status in older people

Serum albumen is the most widely used laboratory indicator of nutritional status, even though it is influenced by a wide variety of acute and chronic inflammatory and malignant conditions. Aging, as well as hepatic and renal dysfunction, can result in low serum albumin levels. In addition, serum albumin has a long half-life of 18 days. Although low serum albumin is rarely the consequence of a poor nutrition status alone, it can serve as a marker of disease severity, which is risk factor for malnutrition. Transferrin, transthyretin, retinol-binding protein, and insulin growth factor-1 are useful alternative measures, but these tests may not be available in some countries and are often expensive. Significantly, laboratory investigations are not essential to diagnose malnutrition. Weight loss and anthropometric data are more closely associated with life-threatening complications among older people in hospital than either albumin or transthyretin [20].

Bioelectrical impedance analysis and dual-energy X-ray analysis measurements are often used in research into body composition, but are rarely if ever used in routine clinical practice.

18.7 Brief review of nutritional guidelines

A number of reviews of diabetes-related nutritional guidelines, including for older people, have been conducted, for example by the American Diabetes Association (ADA) [48], the International Diabetes Federation (IDF) [49], ESPEN [50], ASPEN [51] and the National Institute of Clinical Excellence (NICE) [52]. However, the advice is often the same advice for all

adults with diabetes and not tailored to older people. Some advice may need to be revised to include important factors, such as functional and mental capability, oral health and swallowing problems, and polypharmacy. The Australian Department of Health comprehensive document *Best Care for Older People Everywhere* [5] describes key nutrition facts but also encompasses standards and policies to support good nutrition in hospitals, aged-care homes and the community, including suggestions to enhance communal dining, and provides an audit tool to monitor compliance.

For example, the ADA position statement concerning nutritional interventions for older adults with diabetes mainly focuses on weight management and physical activity, and recommends multivitamin supplements for older adults with reduced energy intake. Likewise, European recommendations are based on studies in younger age groups and then extrapolated to older people. They recommend energy balance, weight control, and a wide variation in carbohydrate intake for adults with diabetes to achieve "good diabetic control."

However, the aim might not be to achieve "good diabetic control" for older people, especially those at high risk of hypoglycemia, falls, and functional deficits. Managing CVD and nephropathy risk might be more beneficial. The individual's quality of life of must be considered when deciding the nutrition objectives and plan, which must be decided with the individual and/or their family.

18.8 Current dietary recommendations: Applications to older people with diabetes

The National Diet and Nutrition Survey of people aged ≥65 years [53, 54] showed that 75% of community-dwelling older people were overweight or obese compared to 3% of men and 6% of women in the community who were under weight. However, 17% of older people in institutions were under weight. An estimated 26% of acutely ill older people in hospital were under-nourished [53].

The following issues need to be considered when deciding a person's nutrition status: body weight, physical activity, and the micronutrient (vitamins and minerals), carbohydrate, protein, alcohol, and sodium composition of the diet. Under-nutrition is as much a concern in older people with diabetes as obesity [20, 54, 55]. Nutrition counselling based on a thorough assessment is essential to managing under- and malnutrition and often needs to include the family, especially if the individual has cognitive impairment or functional deficits that affect their self-management capabilities, such as shopping and cooking.

Many people with diabetes are deficient in micronutrients such as phosphate, chromium, and zinc, which are essential to insulin action. Thus, deficiencies in these micronutrients could contribute to hyperglycemia by reducing insulin sensitivity, although it is not clear whether micronutrient supplements improve insulin sensitivity.

18.9 Energy intake: Carbohydrates and fats

18.9.1 General recommendations

A dietitian with expertise managing older people with diabetes should be involved in educating the older person with diabetes and their families about their diet and in undertaking nutrition assessments and goal setting.

The basis of dietary recommendations for older people with diabetes is extrapolated from research in younger people and clinical expertise. Total dietary energy should be the same for older people as for their younger counterparts, unless the person is overweight or gaining weight, when it might be necessary to reduce the energy intake. However, merely reducing energy intake without increasing activity and determining other factors that contribute to weight gain is unlikely to be successful and may be unsafe.

An acceptable carbohydrate range is generally 45–60% of the total energy [56]. The recommended combined total energy intake of carbohydrate and monounsaturated fat with *cis*-configuration fatty acids is 60–70%. Generally, simple carbohydrate does not significantly affect glycemic control if it is consumed in moderation *with* meals. However, carbohydrates rich in fiber and those with a low glycemic index are preferred. Sucrose intake should not exceed 10% of the total energy intake. Most carbohydrates should come from fruit, vegetables, and legumes.

Generally recommended fat intake is 25–35% of total energy. Monounsaturated fatty acids (MUFAs) with *cis*-configured fatty acids in combination with carbohydrate

should provide 60–70% of the total energy. One portion of oily fish per week and other plant sources are recommended sources of omega-3 fatty acids. Less than 7% of the total energy intake should be from saturated and *trans*-unsaturated fatty acids [48], and polyunsaturated fatty acids should not exceed 10% of the total energy. However, supplemental fish oils and pharmacological doses of vitamins are only recommended when there is a specific indication for the individual.

The daily cholesterol intake should not exceed 200 mg. Plant sterol and stanol esters block the intestinal absorption of dietary and biliary cholesterol. A daily intake of 2 g of plant sterols and stanols lowers plasma and LDL-cholesterol in the general public and in individuals with type 2 diabetes [56, 57]. If these products are used, they should be substituted for rather than be added to the diet to limit weight gain. Fat sources, including oils, should ideally be unsaturated, for example olive, corn, canola, and some varieties of safflower and sunflower oils. Complex carbohydrates, that is, those with long glucose polymers found in starches such as rice, potatoes, and vegetables, should be used instead of simple sugars, which have a bigger impact on blood glucose.

"Diabetic" foods are not recommended, although non-nutritive sweeteners are an acceptable alternative means of sweetening food and drinks. The Dietary Approaches to Stop Hypertension (DASH) diet [58] is appropriate for older people with hypertension and to manage hyperglycemia. The basis of DASH is fruit and vegetables, low-fat dairy products, whole grains, poultry, nuts, and low amounts of fat, red meat, sweets, and sugar-containing beverages.

18.9.2 Malnourished people with diabetes

Providing palatable sugar-containing food may help to stimulate the appetite when people eat very little but it is important to remember that many people do not have a "sweet tooth" in which case a savory alternative might be preferred. The underlying cause/s of poor appetite need to be explored and managed if possible, for example depression, oral health problems, medicines, cognitive impairment, and social issues.

Including small amounts of high-fat food in the diet can help increase energy intake. Conversely, including high-fiber complex carbohydrates can reduce food intake by causing early satiety. Providing extra high-protein and energy snacks may be sufficient to meet an individual's nutritional requirement [59]. These dietary modifications are likely to increase the intake of simple sugar and the glycemic index of the diet; these potentially adverse changes must be considered in light of the safety and other risks associated with malnutrition. Some high-energy foods have a low glycemic index, for example ice-cream, custard, yoghurt, sponge cake, and muffins, which might be appropriate for some older people because they have less effect on the glycemic response.

18.9.3 Obese older people with diabetes

Many older people with type 2 diabetes are overweight or obese; usually blood glucose, blood fats and insulin sensitivity improve with some weight loss. Thus, reducing high-fat foods and simple carbohydrates, and increasing activity are important if the nutritional goal is weight loss and losing weight will not compromise the individual's safety and protein and muscle stores. Fat intake should be limited because it contains over twice as many calories as carbohydrate and protein per gram. Alcohol is also high in calories and has other safety risks that need to be considered.

Reducing the intake of simple sugars, for example by drinking water and substituting diet drinks for high-sugar drinks, significantly reduces calorie intake. Low-carbohydrate diets, <130 g carbohydrate per day, are not recommended for older people with diabetes. Although they lead to short-term weight loss, actually maintaining weight loss is similar to weight loss with low-fat diets. The impact on the CVD risk profile is uncertain.

18.10 Activity and exercise

The benefits of exercise for people with and without diabetes are well documented irrespective of body weight or age. Exercise reduces metabolic and cardiovascular risk, and improves strength, flexibility, balance, and function [60]. An 8-year prospective NHIS study of adults with diabetes (n = 2896) who walked for at least 2 hours per week had 39% lower all-cause mortality rate and 34% reduction in CVD-related deaths. The magnitude of these effects persisted after controlling for age, gender, obesity, functional limitations, duration of diabetes, and/or the presence of other co-morbid conditions [61]. Physical activity also increases insulin sensitivity.

Current guidelines from the Centers for Disease Control and Prevention [62] recommend people should undertake 30 min of moderate activity on most days and indicate that that goal is achievable for many older people. However, the exercise program needs to be individualized to take account of the risks and benefits, and with suitable education to reduce risks such as hypoglycemia, falls, and dehydration in some countries. Older people should have a health check before commencing an activity program, start slowly, and gradually increase to their recommended activity intensity and frequency. Even very frail older people can manage some activities such as walking and chair exercises, which improves their strength over time.

ZUMBA GOLD© [63] is an innovative activity based on Latin and other dance rhythms. It was trialed with people with limited mobility while they received renal dialysis, most were over 60 and many had diabetes. A trained instructor guided people through shoulder, arm, and leg movements, which were modified to suit each individual. The program enhanced fitness, wellbeing, and satisfaction with no detrimental effects on dialysis [63].

18.11 Protein

Protein intake should comprise 10–20% of total energy. The prevalence of nephropathy in older people with diabetes has increased over the past 20 years, possibly due to improved CVD and hypertension management, which means more people with type 2 diabetes live long enough to develop nephropathy and end-stage renal failure (ESRF) [49].

Waugh *et al.* [64] undertook a systematic review to examine the effect of protein intake of between 0.3 and 0.8 g/kg body weight/day. High-protein diets contributed to the development of nephropathy. Reducing protein intake appeared to slow the progression to renal failure, although the optimal amount of protein restriction required and the acceptability to patients is unknown. These findings were controversial. Current protein guidelines mainly concern individuals with type 1 diabetes and often younger people with type 1 diabetes, and often use proxy indicators of protein intake such as creatinine clearance rather than hard clinical end-points such as time to dialysis or death from ESRF.

Current European guidelines recommend that people with diabetes and microalbuminuria or established nephropathy should only consume protein at the lower end of the normal range, 0.7–0.9 g/kg^1 body weight/per day. Consuming less protein than the recommended range increases the risk of malnutrition, especially during chronic illness or catabolic states. The balance between the risk of malnutrition and the possible benefits of reducing protein intake to delay nephropathy must be carefully assessed against the risks, including delayed wound healing and loss of muscle mass and sarcopenia, and frailty.

18.12 Fiber

Fiber is a particularly important dietary component for older people. Soluble fiber, such as oats, bran, pectin, and guar, lowers blood glucose and may improve the profile. Soluble fiber does not appear to interfere with the absorption of minerals in older people with diabetes. *Constipation* is common among diabetics: increasing fiber in the diet helps reduce laxative use, thereby reducing medicine-related risks and improving bowel function.

The ADA [48] recommended fiber intake is 14 g per 1000 kcal. The best sources of fiber are whole grains (insoluble fiber). High-fiber foods are generally more satisfying and should be used with caution in those with a poor appetite. Very high-fiber diets in very old people could contribute to fecal impaction if not enough liquid is consumed.

18.13 Sodium

Taste and smell are important to food enjoyment. They decline with age, beginning around age 60 and becoming more marked after 70. Salt and monosodium glutamate are commonly added to foods to enhance taste, and can improve food intake in older people. However, high sodium intake is linked with the development or exacerbation of hypertension. Reducing salt intake is one management strategy. Using flavor enhancers to encourage food intake for underweight people needs to be balanced against exacerbating hypertension and its related risks. Generally salt intake should be <6 g per day [48, 49].

18.14 Alcohol

Older people are more susceptible to the adverse effects of alcohol and are likely to develop problems at relatively low amounts of alcohol due to age-related changes in body composition. However, moderate amounts of alcohol appear to benefit blood pressure and glycemic control, and reduce the risk of thrombosis. Alcohol can also act as an appetite stimulant, which may be beneficial for older people with poor appetite and undernutrition. Large quantities of alcohol increase the risk of stroke, hypertension, hypoglycemia, and lactic- and ketoacidosis [65]. Recommended alcohol intake should not exceed 1–2 units per day for women and 1–2 units per day for men on 2–3 days/week. Alcohol should not be consumed when driving or with some medicines.

If people are prescribed insulin or sulfonylureas they should be advised to adhere to recommended alcohol intake and about the risk of hypoglycemia associated with alcohol and advised to consume carbohydrate-containing foods when they drink alcohol to reduce the risk of hypoglycemia. Alcohol impairs judgment and problem-solving, and can affect other aspects of cognition, putting the individual at considerable risk. In addition, hypoglycemia can be mistaken for intoxication and appropriate treatment delayed or not instituted, with disastrous effects [65].

18.15 Vitamins and minerals

Older people with diabetes are at risk of micronutrient deficiency due to inadequate food intake, consequences of chronic disease, or medicines [66]. The second evaluation of the Euronut-SENECA study population occurred in 1993 in people aged 74–79 years (n = 1005) [67]. Overall, 23.9% of men and 46.8% of women had low dietary intake of at least one of the following micronutrients: calcium, iron, retinol β-carotene thiamine, pyridoxine, and vitamin C. The clinical significance of these findings is not clear.

Vitamin D plasma levels were low in 36% of men and 47% of women and cobalamin deficiency occurred in 23.8% of both genders. Many older people in aged-care homes and hospital have more micronutrient deficiency than their community-dwelling counterparts, especially of thiamine, pyridoxine, cobalamin, folate, vitamin C, vitamin E, and selenium. In addition, between 10% and 40% have multiple vitamin deficiencies, and 10% are anemic [68]. Anemia can contribute to tiredness. Long-standing anemia can lead to lower than actual HbA1c levels [69].

There is limited information about whether routinely adding supplements to the diet is beneficial and some confer risks such as constipation (calcium). Some minerals are required to enhance the absorption of others, for example vitamin D enhances calcium absorption, thus they need to be given together. In addition, consuming more than the recommended daily requirement can lead to hypervitaminosis and high mineral levels, which can compromise health.

18.16 Specific mineral and vitamin deficiencies

Vitamin D and calcium are essential for bone homeostasis. Vitamin D is necessary to active calcium absorption from the gut and to normalize parathyroid hormone levels [70]. Vitamin D deficiency contributes to osteomalacia, osteoporosis, rickets and myopathy, impaired mobility, and increased rate of falls and fractures. Mobility declines markedly when serum 25-hydroxyvitamin D is <40 pmol/l[1]. Vitamin D supplementation can reduce the fall rate in residents in aged-care homes, even for residents who are not deficient in vitamin D. People over age 70 with increased frailty fracture risk benefit most from vitamin D supplements [70]. Vitamin D deficiency predicts falls and fragility fractures, and increases the risk of other morbidities and death [70]. Generally calcium is needed to improve vitamin D absorption and bone health should be monitored regularly.

Osteoporosis is a major health issue, with increasing prevalence as the global population ages. The older the individual is the greater is their risk of osteoporosis and falls. People over age 75 are at increased risk of fragility fractures and other adverse outcomes and benefit most from treatment, but they are often not adequately assessed or treated [71, 72]. *All* older people should be carefully assessed and treated according to their individual risk profile. Management is multifactorial, and co-morbidities and life expectancy need to be considered before initiating medicines, including vitamin D, and regularly after treatment is initiated [73]. Although evidence in older people is limited, several

medicines can effectively reduce the risk of osteoporosis in older people.

Treatment with vitamin D at dosages of 700–800 IU/day, with or without calcium, reduced the relative risk for hip and other non-vertebral fractures by 23–26% compared to calcium or placebo in ambulatory older people and those in aged-care homes [70, 71]. Plasma 25-hydroxyvitamin D <40 nmol/l (or <16 μg/l) is indicative of vitamin D deficiency and needs to be treated. However, if vitamin D deficiency was defined a serum 25-hydroxyvitamin D < 80 nmol/l, a much larger proportion of the population would meet the criteria for vitamin D deficiency.

Most circulating 25-hydroxyvitamin D derives from exposure of the skin to UV-B radiation in sunlight, the remainder is obtained via the dietary intake of foods rich in vitamin D (predominantly oily fish), supplements, and vitamin-D-fortified food. Dietary requirements are greater in older people due to reduced production in the skin, decreased sun exposure, age-related thinning of the skin, and other skin changes. For that reason the recommended dietary reference intakes are higher for older adults; in the USA, it is 10 mg (400 IU) for people 51–70 years of age. The USA and Canada have mandatory vitamin D fortification of milk and Canada also requires it in margarine, whereas other countries have variable levels of non-mandatory fortification [71–73].

Vitamin D therapy is safe, inexpensive, and easy to administer. The prevalence of vitamin D deficiency is so high among older people in hospitals and aged-care homes that routine supplementation with doses of 800–1000 IU/day, without testing, is being recommended and increasingly adopted. The most effective form of replacement is oral cholecalciferol, which can be given in intermittent boluses at intervals of 1–6 months, in doses not usually totaling more than 50 000 IU/month or as 500–2000 IU/day [70].

Calcium works with vitamin D and hormones such as PTH to optimize bone health. Few older people achieve an adequate daily calcium intake (1200 mg) without taking a calcium supplement; the median daily dietary intake for American men and women aged ≥60 years is approximately 600 mg [74, 75]. A daily tablet supplement of 500–700 mg of elemental calcium is usually sufficient to achieve adequate calcium intake. However, people with low dietary intake should take two tablets.

The risk of fractures due to falls and osteoporosis in older people with diabetes may be exacerbated by peripheral neuropathy, autonomic neuropathy, hypoglycemic episodes, and vision deficits. Sunlight on the skin should be sufficient for vitamin D synthesis for most adults if the face and arms are exposed for 30 min/day. However, even in countries with high levels of sunlight, like Australia, vitamin D deficiency is common because of the "slip, slop, slap" campaign to reduce skin cancer [70]. It is also common in Muslim cultures where women are fully covered.

Vitamin B_{12} (cobalamin) deficiency is more common in older than younger people and can contribute to frailty, especially in community-dwelling older women [76]. Vitamin B_{12} is associated with demyelination disorders of the nervous system and hyperthromcystcinemia, and, with concomitant folate deficiency, increases the risk of megablastic anemia [70].

In the Framingham study, 11.3% of older people had a serum vitamin B_{12} concentration <258 pmol/l and elevated plasma homocysteine and methylmalonic acid levels compared to 5.3% of younger adults. The prevalence can reach 30–40% of older people living in aged-care homes. The signs and symptoms of vitamin B_{12} deficiency often are subtle, for example macrocytic anemia, subacute combined degeneration of the spinal cord, neuropathies, ataxia, glossitis, and possibly dementia, thus there should be a low threshold for testing in malnourished older people, those who have neurologic or neuropsychiatric conditions consistent with vitamin B_{12} deficiency, and those in aged-care homes and psychiatric hospitals [77].

Homocysteine damages blood vessel walls and there is a significant association between increased plasma homocysteine levels and increased risk of CVD, disability, and all-cause mortality [78]. The most common cause of deficiency in older people is malabsorption of cobalamin from food and pernicious anemia, which account for approximately 60–70% and 15–20% of cases, respectively [78]. Both, vitamin B_{12} and folate deficiencies frequently coexist in older people. Gastric atrophy is the most common predisposing factor and is present in more than 40% of people aged >80 years. Numerous factors predispose to the development of gastric atrophy, including *Helicobacter pylori* infections, chronic alcoholism, bacterial overgrowth, the long-term ingestion of metformin and antacids, and gastric bypass surgery for obesity.

Clinically apparent causes should be treated when possible, but a reversible cause of vitamin B_{12} deficiency often is not found, consequently vitamin B_{12} usually needs to be continued for life. The recommended daily intake of vitamin B_{12} is 2–5 mg in older adults. Vitamin B_{12} deficiency (<150 pmol/l) due to inadequate dietary intake is best treated initially with intramuscular vitamin B_{12} or at least with 100 mg per day of oral vitamin B_{12}. Deficiency due to malabsorption is best treated with intramuscular vitamin B_{12} or possibly high-dose oral vitamin B_{12} (e.g., 500 mg per day), whereas pernicious anemia requires lifelong intramuscular therapy [79]. When folate and vitamin B_{12} deficiency coexists, vitamin B_{12} should be given with appropriate folate doses or a multivitamin that contains folate should be co-administered.

Folate-rich foods include orange juice, dark green leafy vegetables, peanuts, strawberries, dried beans and peas, and asparagus. The synthetic folic acid found in vitamin supplements and fortified foods is absorbed more readily than folate from food. The recommended daily intake of folate and folic acid is 400 mg. The upper limit is 1000 mg of synthetic folic acid, which can mask the features of coexistent vitamin B_{12} deficiency in high doses in older people. Folate deficiency causes macrocytic anemia, increases homocysteine levels and rates of colorectal cancer, and possibly increases cervical cancer, cognitive impairment, depression, and dementia.

The prevalence of folate deficiency among older people varies from 4% to 50%, depending on the population, and is particularly common among people living in institutions. Most folate deficiency results from inadequate dietary intake, impaired absorption due to some medicines such as methotrexate, anticonvulsants, and sulfasalazine, and high alcohol consumption. When folate deficiency is due to diet, it might be possible for the older person to increase their intake of fruit and vegetables, and this is the first-line treatment. Folic acid supplements (0.5–5 mg per day) are essential when diet is not the cause or cannot be changed [80].

18.17 Other vitamins and minerals

The following information is based on Joshi & Morley (2006) [81].

- **Zinc** (Z) deficiency is associated with a wide variety of abnormalities, including anorexia, T-cell abnormalities, wound healing, impotence, and, possibly, macular degeneration. There is currently no definitive evidence that Z deficiency causes diabetes or affects glucose homeostasis despite its role in insulin action. The recommended daily allowance (RDA) for Z for men aged >50 years is 15 mg/day and 12 mg/day for women aged >50. People with leg ulcers, erectile dysfunction, or poor wound healing might require a 3-month course of Z supplements consisting of 70 mg elemental Z/day.
- **Chromium** (Cr) plays an important role in regulating glucose and lipid metabolism. Symptoms of deficiency include weight loss, neuropathy, and impaired glucose tolerance. The prevalence of Cr deficiency in people with diabetes is uncertain. Cr supplements enhance glucose tolerance in people with diabetes, but the significance of this finding in older people with diabetes is unknown.
- **Copper** (Cu)'s role in older people with diabetes is still unknown. The recommended daily intake of Cu is 1.5–3.0 mg.
- **Iron** (Fe): Currently, there is no evidence of major alteration in iron status in people with diabetes unless they develop renal failure. Although the iron status in older people with diabetes requires more research, they do not appear to be at risk of iron deficiency unless the established causes of iron loss, such as hemorrhage, are present.
- **Magnesium** (Mg) plays an important role in glucose homeostasis. Diabetes is associated with increased urinary losses of Mg, especially when hyperglycemia is present, and especially in older people. The intake recommended for healthy adult males is 420 mg/day and 320 mg/day for women.
- **Vitamins A and B** are essential to a variety of metabolic functions. The primary source of these vitamins is green leafy vegetables. People with neuropathy participating in a 2-month trial of vitamin B_1 or B_6 suggested some benefit of supplementation but more research is needed. No deficiency in vitamin A has been demonstrated in older people.
- **Vitamin C** deficiency is common in older and younger people with diabetes. Chronic hyperglycemia depletes tissues stores of vitamin C. Hyperglycemia is associated with impaired leukocyte function and microangiopathy. The current UK recommended daily intake of vitamin C is 40 mg. Routine supplementation is not recommended. The vitamin C daily requirement was based on the need to prevent scurvy;

further research into the risks and benefits of higher vitamin C intake is required. The ADA does not recommend routine supplementation with antioxidants such as vitamins E and C and carotene because of the limited evidence for benefit and concerns about long-term safety, with the exception of older peoples with low energy intake who might benefit from daily multivitamin supplements.

18.18 Oral nutrition supplements

The first step in deciding whether supplements are required is to identify people at risk of or with actual nutrient deficiencies, and which food ingredients they are deficient in. It is also important to identify issues that can be remedied, including social and environmental issues. Oral supplementation can increase both energy and nutrient intake in older people [50]. Oral supplements should be given at an early stage of declining nutritional status such as insufficient intake, weight loss >5% in 3 months or >10% in 6 months, or when the BMI is <2 2 kg/m^2.

A wide variety of sweet and savory oral supplements in various formulations, such as powders, pre-made carton sip feeds, glucose polymers in powders and syrups, and protein powders, is available. They can be useful if the person can still eat but is struggling to achieve adequate nutrition, and can reduce mortality and complications among under-nourished people in hospital [82]. There also is a trend towards a shorter length of stay in hospital for people given supplements. The lowest mortality is in people aged >75 years, those taking >400 kcal of supplement/day, those with poor general health, and those who were initially under-nourished. However, there is a tendency for initially well-nourished people in hospital for more than 4 weeks to become malnourished [82]. Supplements might help prevent the decline in nutrition status in hospital.

Supplements should be prescribed for a limited period of time and continued only after a beneficial effect is demonstrated for most people. Adherence to and acceptance of supplements may become problematic for a range of reasons, which should be explored before commencing supplements. Supplements should be given between meals and occasionally before bedtime to limit the effect on food intake. Consumption of each supplement should not exceed 30 min and it should ideally be managed, monitored, and documented by the nursing staff, for example during medicine rounds. For most supplements, 1 ml is equal to 1 kcal, but hypercaloric drinks (1.5–2 kcal/ml) are available and might be useful under certain circumstances. High-protein supplements might be beneficial if the individual is protein deficient. A realistic goal for energy intake from nutritional supplements is 400 kcal/day, although some older people might need 600 kcal/day.

The high sugar content in many supplements is often offset by the individual's low carbohydrate intake and can be help prevent hypoglycemia during periods of poor oral intake. Spicy snacks are sometimes helpful and induce older people with impaired taste to eat more [58]. Readily available finger-food that older people in aged-care homes can help themselves to as they wish improves total intake in ambulant people with dementia in aged-care homes who forget meal times and wander during formal meal times [5].

18.19 Prebiotics and probiotics

Aging has a significant effect on the homeostasis of intestinal flora. Probiotics such as *Lactobacilli* and *Bifidobacteria* are part of the normal human intestinal flora and with prebiotics or non-digestible oligosaccharides appear to be useful to prevent some health problems and promote some aspects of health in older people [83]. More research is needed but they may be particularly useful older people who are malnourished and those with lactose intolerance or problems absorbing calcium, and to boost immunity. Under-nourishment leads to damage in the epithelium in the intestinal tract, which results in reduced gut-mediated immunity, affects the absorption of essential diet components, and reduces appetite. Probiotics such as yoghurt help normalize nutritional status in children and may have similar benefits for older people [83].

Prebiotics such as lactulose and inulin in large doses (10–40 g/day) can positively affect calcium bioavailability and reduce constipation because they act as dietary fiber. Probiotics may help prevent and treat antibiotic-related diarrhea [83]. Several studies show that probiotics stimulate the immune system in older people by increasing *a*-interferon, total lymphocyte count, circulating CD4+ and CD25+ cells, and NK tumoricidal activity, especially in people over age 70 [83].

18.20 Artificial nutrition

The nutritional management of older people with diabetes in hospital includes managing hyperglycemia and its effects on nutritional status, the metabolic consequences of stress, and specific nutrient mixes [84]. Artificial nutrition support can also contribute to hyperglycemia during stress, injury or illness in people with established diabetes and unmask glucose intolerance in people with pre-diabetes. Enteral and parenteral nutrition can be used to provide nutrition support for malnourished older people in aged-care homes, in hospital, and at home. The indications and complications are similar for other patients but the benefits might include improved function and quality of life for older people with diabetes.

Hyperglycemia has a detrimental effect on the immune system and adversely affects chemotaxis, granulocyte adhesion, phagocytosis, intracellular killing, and complement function [85, 86]. The optimal blood glucose level for ill patients receiving nutritional support is unclear: various experts have suggested different blood glucose targets and approaches to avoid both hyper- and hypoglycemia. The specific glycemic targets must be tailored to the individual's needs considering age, prognosis, underlying cause/s of the hyperglycemia, functional and cognitive status, severity of any infection, degree of metabolic stress, and immune status (see Chapter 2).

Hyperglycemia alters fat metabolism and results in dslipidemia, but lipid targets associated with nutritional support in people with diabetes vary. The degree of dyslipidemia is frequently disproportional to the degree of hyperglycemia and should be monitored and treated in its own right (see Chapter 26). Clinical consequences of hyperlipidemia include impaired immune response, endothelial dysfunction, increased risk of coagulopathy, and exacerbation of insulin resistance.

Every hospital and aged-care home and homecare service that provides nutrition support for older people should have clear guidelines, policies, and procedures that describe the requirements and monitoring processes to be implemented when nutritional support is implemented [5, 87]. The monitoring frequency depends on the clinical situation and must be individualized. People with hyperglycemia and those who are severely malnourished should be monitored frequently to detect metabolic complications early and enable early management. Serious complications include life-threatening re-feeding syndrome, which is associated with profound electrolyte disturbances and fluid overload.

During re-feeding the metabolism switches from fat to carbohydrate and stimulates increased insulin release. During carbohydrate repletion, insulin-stimulated glucose uptake is accompanied by increased cellular uptake of potassium, phosphorus, and water. Magnesium requirements increase as the sodium–potassium adenosine triphosphatase (ATPase) pump is stimulated [9]. However, older people with long-standing type 2 diabetes usually have beta-cell exhaustion and are unable to produce a significant amount of insulin, and people with type 1 diabetes do not produce insulin.

It is important to manage the blood glucose and perform regular blood glucose tests to prevent hyperosmolar states as well as ketoacidosis and their consequences. The medicine regimen must be tailored to suit the individual and might include oral or injectable glucose-lowering medicines or insulin. Insulin is required for all patients with type 1 diabetes and for those with type 2 diabetes with significant hyperglycemia or critical illness. The type of insulin regimen needs to be tailored to the individual's needs. It should be noted that if insulin is added to a parenteral nutrition bag, some will be adsorbed onto the plastic of the bag and cannulas.

18.21 Is artificial nutritional support necessary?

Artificial nutritional support is indicated in older people who are malnourished or who would become malnourished if they were not given artificial nutrition support. However, life expectancy and the benefits and risks must be considered (Chapter 21). People need to be artificially fed for 7 or more days to derive benefit [88]. The goals of nutritional support are to maintain or improve nutritional status, promote wound healing, optimize glycemic control and lipids, and avoid hyper- and hypoglycemia.

Factors such as potential social isolation, depression, effect on quality of life and the fact that the nutritional support might not prevent malnutrition, the risk of pressure ulcers and infection around tube insertion sites need to be considered. Likewise, people who are confused or become delirious might dislodge nasogastric tubes, which would put them at risk of pneumonia and death.

It also increases the carer burden if the older person lives at home and may have adverse effects on the individual's mental health, body image, and willingness to socialize [89].

18.22 Delivery routes for artificial nutritional

The optimal route must be decided with the individual and often their family when nutritional support is indicated. Enteral nutrition should be used when possible because it has many advantages over parenteral nutrition, including cost benefits, lower risk of infection, and more physiological effect on intestinal microorganisms.

Enteral nutrition is suited for people with diabetes because it delivers nutrients in a more physiological way. Oral dietary supplementation should be tried first and enteral nutrition considered only if the individual is at risk of aspiration or cannot meet their nutritional requirements orally. The decision should be made with the individual and their family (or proxy decision makers at the end of life; Chapter 36) as well as with the management team. The options include pre-pyloric or post-pyloric tube feeding in the short term.

When enteral nutrition is needed for longer periods, for example due to dysphagia, percutaneous endoscopic gastrostomy (PEG) is often the route in older people. Three groups can be identified:

1 People with diabetes who need prolonged home enteral nutrition, for example due to persistent dysphagia.
2 People who will derive short-term benefit from enteral nutrition before resuming oral nutrition, such as those with secondary anorexia after stress.
3 People who require long-term enteral nutrition due to their primary disease, where enteral nutrition is palliative. Plans for managing enteral feeds when the person is entering the terminal stage of their life should be discussed with them when the feeds are commenced and their preferences documented in their advanced care plans.

As might be expected, life expectancy and health-related quality of life are poorer in older people receiving nutritional support than in younger people, and life expectancy is shorter when older people have home enteral nutrition [5] and after procedures such as PEG tube insertions [89, 90]. There are no studies that demonstrate any benefit of artificial nutrition compared to no nutritional support in comparable groups, for obvious ethical reasons. Existing studies are observational or do not compare groups and provide conflicting results.

18.23 Enteral tube feeding

Enteral tube feeding (ETF) can be continuous, intermittent or delivered overnight [5, 50, 51]. Deciding the feeding regimen includes discussing the type of enteral tube feed needed to safely deliver the nutritional and fluid requirements. The approximate composition of commonly used feeds is as follows:

- Standard enteral tube feeds (1 kcal/ml; osmolarity 201–250 mOs/l): These contain 15–16% of energy as whole protein (milk protein-casein), 30–35% of energy as a mixture of long- and medium-chain fats (40% MUFAs, 30% short-chain fatty acids (SFAs) and poly-unsaturated fatty acids (PUFAs) such as linseed, sunflower, safflower or rapeseed oil, and may also contain fish oil. Carbohydrates provide 50–56% of the energy content of the feed, mainly present as maltodextrins, but may also contain sucrose, oligosaccharides, polysaccharides, corn syrup, and starches. Standard formulas are often used when commencing enteral feeds. The high carbohydrate and low fiber content can increase postprandial blood glucose because of the rapid transit time and insulin might be required to keep the blood glucose in the individual's target range [91, 92].
- High-energy feeds (1.5 kcal/ml; osmolarity 300 mOs/l): These have the same percentage energy from macronutrients as the standard formula. The osmolarity of these products is higher, 300 mOs/l, due to the reduced volume of the product.
- Fiber feeds: The amount of fiber per 100 ml is usually between 1 and 2 g. The type of fiber includes soy, inulin wheat fiber, fructo-oligosaccharides, oat fiber, and gums, from a mixed or single source. The ratio of soluble to insoluble fiber in the mixed fiber source feed varies: some products are 50/50 while others contain 75% insoluble and 25% soluble fiber.
- Specialist feeds: These are used to manage people with special needs such as those with renal failure, malabsorption, electrolyte restrictions, lactose intolerance or inflammatory bowel disease [16, 92–96].

As a general rule, elemental or semi-elemental feeds have an osmolarity between 300 and 500 mOs/l. Specialist formulas for people with diabetes with a lower glycemic load, lower glycemic index, and less carbohydrate include:

- Nutrison low energy for diabetes
- Nutrison for diabetes
- Diasip
- Glucerna
- Resource diabetic Complete modified
- elemental and sub-elemental formulas for people with gastroparesis.

In addition, specialized supplements are available for people with pulmonary disease, renal disease, cachexia associated with cancer, and metabolic stress, as well as predigested elemental formulas and products to support wound management such as Cubitan, Recover, and resource Arginaid [16].

18.24 Composition of specialist feeds to manage hyperglycemia

Most of the evidence for using specialized diabetes enteral feeds to manage hyperglycemia has been extrapolated from the general diabetic literature. Specialist feeds for people with diabetes were formulated with lower liquid carbohydrate content than standard feeds (>50% of calories as carbohydrate), which has less impact on blood glucose. As indicated, tube feeding is associated with a more rapid rise in postprandial glucose than solid diets with a similar nutritional composition [96]. High postprandial glucose levels predispose to hypertriglyceridemia [94].

Compared with standard formulas, diabetes-specific formulas are typically higher in fat (40–50% of energy, with a large contribution from MUFAs, e.g. >60% of fat), with a lower carbohydrate content (35–40% of energy) and up to 15% of energy from fructose. These nutrients can delaying gastric emptying (fat and fiber), delay intestinal absorption of carbohydrate (fiber), and have less effect on blood glucose (fructose). A high proportion of MUFAs can also have beneficial effects on lipid profiles.

Only short-term studies have been undertaken using specialized oral diets in which the carbohydrate content is reduced by increasing the MUFA content. These studies were undertaken either as single test meals or over short periods of time and involved relatively few participants.

Many of the nutrients included in tube feeds must be chemically modified to enable them to be delivered through a tube. The glycemic response of a food depends on its physical properties, thus changing nutrients from a solid to a liquid can radically alter the glycemic properties. There is good evidence for a beneficial effect of fiber in a solid diet; the benefits of adding fiber to a liquid diet are unclear [86]. In addition, adding fiber to tube feeds can be problematic because some fiber blends increase the viscosity of the feed, which makes it extremely difficult to deliver the formula through fine-bore feeding tubes. The biophysical properties of a fiber in a liquid may be one reason why glycemic control does not improve with tube feeds containing fiber, that is, the postprandial insulin and glucose responses are related to the carbohydrate load in tube feeds, and not to the fiber content.

Pohl *et al.* [91] undertook a meta-analysis of studies where participants had a medium age of 70 years, insulin-treated type 2 diabetes, HbA1c < 7.0%, and the indication for tube feeding was dysphagia caused by neurological disorders. They found diabetes-specific oral and tube formulas containing high proportions of MUFAs, fructose, and fiber were associated with improved glycemic control compared to standard formulas. The diabetes-specific formulas, given orally as nutritional support or via ETF, resulted in a significantly lower postprandial rise in blood glucose, peak blood glucose concentrations, and lower glucose-versus-time area under the curve in people with diabetes without evidence of hypoglycemia. Pohl *et al.* suggested that glycemic control can be acceptable using diabetes-specific enteral formulas compared to standard formulas.

Many studies show a strong association between postprandial glucose regulation and cardiovascular complications in people with diabetes, impaired glucose tolerance, and all-cause mortality, whereas no such association was found with fasting glucose control [48, 53, 88]. This implies that improving glycemic control might reduce cardiovascular complications in people with diabetes, although that hypothesis was not assessed in the studies reviewed. In addition, many older people with diabetes are likely to have established CVD and preventing long-term complications is not generally a significant aim, although managing existing complications to achieve comfort and quality of life are important aims.

Sometimes lower doses of glucose-lowering medicines can be used with diabetes-specific formulas and the need for insulin injections might be reduced. Very few long-term studies have been reported examining clinical outcome. One study [85] showed that diabetes-specific formula was associated with a trend towards reduced incidence of pneumonia, fever, and urinary tract infection relative to the standard formula. This finding could be clinically significant because hyperglycemia increases the risk of infections and infections increase the likelihood of hyperglycemia. Other common diabetes complications include CVD and hyperlipidemia. Diabetes-specific formulas have higher fat content than standard formulas, but they do not appear to have a detrimental effect on total cholesterol, HDL-cholesterol or triglycerides.

National organizations [48, 49, 52] generally recommend low-fat (25–35% of energy) and high-carbohydrate diets (45–60%) rich in complex carbohydrates for people with diabetes. The situation for MUFAs is less clear. The ADA indicated there is little evidence that MUFAs exert any long-term effects on glucose control or other metabolic parameters [48]. Formulas that have a particularly high proportion of fructose should probably be administered with caution to critically ill people at risk of hyperglycemia and lactic acidosis. Dietary therapy or ETF delivered under appropriate medical, nursing, and dietetic supervision can be individualized to include more MUFAs when indicated, for example for malnourished people to increase their dietary energy intake [88].

18.25 Administering medicines with enteral feeding

The policies and guidelines of the relevant organization providing care for the individual with diabetes should be followed when administering medicines via tube feeds. Some general guidelines are given below.

- Liquid medicines are preferred to other dose forms.
- Check whether medicines can be crushed or capsules opened. If there are no contraindications they can be crushed and mixed to a fine powder and dissolved in 10–15 ml of water. Most hospitals and aged-care homes have lists of medicines that should not be crushed. These include medicines likely to irritate the gastrointestinal tract and long-acting medicines.
- Stop the feed about 30 min before the medicine administration time and flush with 30 ml water, especially if the medicine needs to be given on an empty stomach. Wait 30 min after administering the medicine before recommencing the feed to enhance bioavailability.
- The medicine and feed regimens need to be reviewed for any actual or potential food–medicine interactions that could compromise the medicine's effectiveness or lead to adverse events. If it is not possible to change either, it might be necessary to stop the feed for longer before and after the medicine is administered.
- Ensure any medicines prepared in syringes are prepared in syringes manufactured for oral use and are clearly labeled.
- Allow the medicines to flow by gravity down the tube. Pushing them through can block the tube [96–98].
- Regular blood glucose testing and monitoring the emerging blood glucose pattern is important when people are receiving enteral feeds. Blood glucose testing is important to detect hypo- and hyperglycemia and to determine the feed and medicine regimens.

18.26 Complications of enteral nutrition

Gastrointestinal problems are the most complications of tube feeding, especially gastroparesis and diarrhea. However, changes in fluid balance and electrolytes, hyponatremia with and without edema, and overhydration also occur [5]. The latter can lead to cerebral edema, which has high mortality rates in older people. Refeeding syndrome is possible, especially in older people with significant nutrition deficits [5]. In addition, 10–30% develop hyperglycemia [5, 90].

Gastroparesis is extremely common among people with diabetes and affects 30–75% of all people receiving enteral feeding [5]. Gastroparesis reduces the tolerance to enteral nutrition and causes bloating, early satiety, nausea, and vomiting. The irregular and unpredictable rate of gastric emptying associated with gastroparesis can result in poor glycemic variability, which can exacerbate gastroparesis. A number of prokinetic medicines can improve gastric emptying in addition to changing the enteral formula. If these strategies are unsuccessful changing to jejunal feeding may be helpful.

Chronic diarrhea occurs in 20–85% of people with diabetes receiving enteral feeding and can be difficult to manage because its management requires a systematic approach, including understanding the individual's bowel history, including altered bowel habits, prior to tube feeding. It is important to consider all possible contributory factors to the diarrhea, note all prescribed and non-prescribed medicines, including broad-spectrum antibiotics, and consider bacterial overgrowth and specific infections in the gut such as *Clostridium difficile* and or other bowel pathology. The enteral feed might also cause or contribute to diarrhea if hyperosmolar feeds or feeds with low sodium content are used and if the feeds are delivered quickly (bolus feeding).

18.27 Parenteral nutrition

Parenteral nutrition is generally not indicated in older people with a functioning gastrointestinal tract. It is associated with higher risk of complications and higher health costs [93]. Parenteral nutrition is only indicated when enteral nutrition is contraindicated, which usually occurs when the gastrointestinal tract is either non-functioning or not accessible, for example approximately 30% of people on parenteral nutrition develop transient diabetes and at least 15% develop hyperglycemia [93, 94, 99]. Intravenous catheter-related infections are five times more prevalent in people receiving parenteral nutrition, and the risk is even higher in the presence of hyperglycemia.

Parenteral nutrition formulae are hyperosmolar and need to be delivered via a large central vein. Central access can be achieved either by a peripherally inserted central catheter (PICC) threaded up into a larger central vein, which is more suitable in the short term, or by direct access into a central vein (PICC <15 cm; Hickman line or Portacath, as long-term lines).

The energy content in parenteral nutrition formulas is from a mixture of fat and carbohydrate (usually 50% non-protein energy from carbohydrate and fat). The fat improves substrate utilization, delivers fat-soluble vitamins, and reduces the osmolarity of feeds, which can be used for simultaneous peripheral feeding. The protein component in parenteral nutrition consists of essential amino acids and soluble, non-essential amino acids.

Parenteral nutrition is usually delivered in one bag. A variety of premixed parenteral formula is available and is designed to meet the nutritional requirements for most people. However, some hospital pharmacies are able to make individual formulas when needed. Parenteral nutrition should be administered continuously over a 24-h period using a suitable infusion pump to minimize infusion errors, and prevent variability in blood glucose and electrolytes, and rapid changes in fluid balance.

Insulin is the preferred method of managing blood glucose when parenteral nutrition is required. Insulin doses must be tailored to the individual and the carbohydrate content in the formula [91] and the blood glucose pattern, which should be tested regularly.

Parenteral nutrition support can be optimized to minimize hyper- and hypoglycemia by adhering to the following points:

1. Prevent overfeeding.
2. Ensure that the infusion rate of carbohydrate in the formula does not exceed the glucose oxidation rate (6–7 mg/kg/min) because exceeding this value may increase the metabolic rate and worsen glucose tolerance. Alternative sugars have been tried experimentally as potential carbohydrate substitutes, including fructose, sorbitol, xylitol, and glycerol, but have not successfully prevented or improved the hyperglycemia.
3. Optimize the fat to carbohydrate ratio. Some experts advocate increasing the fat component to 60–70% of non-protein energy to reduce the carbohydrate component to 30–40% and reduce the risk of hyperlipidemia, which increases the risk of sepsis in critically ill people and can precipitate pancreatitis and renal failure. Reducing the carbohydrate component in people with hyperglycemia reduces the glucose load but not necessarily the need for insulin.
4. Fiber supplementation can improve bowel function and reduce stool frequency and stool consistency without affecting the nutrition during enteral feeding of older people in hospital [100].
5. Gradually reduce the flow rate of the parenteral nutrition and the insulin dose to prevent rebound hypoglycemia before stopping the infusion.

18.28 Ethical issues

The ethical issues associated with enteral feeding need to be considered before commencing artificial nutrition because of the controversy regarding life-sustaining treatment in older people in some countries. The issue

should be discussed as part of care planning for palliative and end-of-life care and documented appropriately (Chapter 36). Informed consent from the individual is essential unless they have nominated a family member or a caregiver as a proxy decision maker. It is helpful to have such discussions early before dementia and other cognitive impairments affect decision making.

18.29 Oral health, swallowing, and dysphagia

Swallowing is a complex process involving the nerves and muscles of the mouth, throat, and esophagus. Difficulty swallowing increases the risk of choking, under- and malnutrition, dehydration, aspiration pneumonia, and oral infections. Dysphagia, which occurs in 40–50% of older people, increases the risk of oral infections, especially when oral hygiene is inadequate. Swallowing can be assessed using the Gagging Swallowing Screen or the Toronto Bedside Swallowing Screen. It is essential to educate the individual, families, and carers about the importance of oral health and regular dental assessments.

Diabetes adversely affects oral health, increasing the risk of gingivitis and other oral infections. Gingivitis is a major cause of tooth loss and pain that can affect oral intake. Poor oral and dental health is linked with chewing difficulties that can cause malnutrition, poor general health, and a reduced quality of life. There are dietary implications for those with no teeth or partial dentures, as difficulties in eating can lead to a reduction in the variety of food choices and an overall reduction in nutrient intake. Full dentures can cause a reduction in food consumption due to the mouth feeling full, a greater time needed to eat, causing embarrassment, and changes in food flavors [101]. All patients should be encouraged to maintain good oral hygiene, with special attention given to those with dry mouths or who eat more frequently due to a small appetite or, in the case of a patient with type 1 diabetes, to a need for frequent snacks. Dental advice is required for patients with chewing difficulties, pain, and other oral health problems.

Nutrition therapy depends on the type and extent of the swallowing disorder. The types of feed include normal food, thickened feeds, liquids of different consistencies, and total enteral nutrition delivered via a nasogastric tube or PEG. Enteral nutrition delivered via a PEG tube improved nutrition status compared to enteral nutrition delivered via a nasogastric tube in a Cochrane analysis of interventions for dysphagia in acute stroke [102]. Dysphagia rarely improves after 2 weeks. If severe dysphagia persists for longer than 14 days after the acute event, a PEG should be placed immediately.

18.30 Pressure ulcers and the diabetic foot

Malnutrition increases the risk of pressure sores, which are associated with an increased risk of morbidity and mortality. Pressure ulcers develop in 4–10% of newly hospitalized patients, increasing to 14% in aged-care homes. Peoples with diabetes are a vulnerable group and often have poor wound-healing capacity. Currently, the evidence for routine micronutrient supplements to improve wound or leg ulcer healing using either multivitamins or vitamin C, with or without zinc, is inconsistent. One study reported improved healing of leg ulcers and wounds following a 3-month period of zinc supplements given as 70 mg of zinc three times each day. A review of nutrition and wound healing concluded that, while routine nutrition supplements in hospital may not be warranted, zinc and vitamin C supplements might be reasonable but vitamin C supplements alone are unlikely to be beneficial [103].

Low protein and energy intake, BMI, and albuminemia are all risk factors for the development of pressure sores in elderly patients. Additionally, oral nutritional supplements could significantly reduce the incidence of pressure ulcer development in at-risk patients (odds ratio 0.75, 95% CI: 0.62–0.89) [98, 99]. As with the effect of nutritional status on the healing of existing pressure ulcers, the scarce amount of available data suggests that malnutrition slows the healing process, and that an increase in protein and energy intake raises the rate of healing. A systematic review by Stratton *et al.* showed that enteral nutritional support may significantly reduce (by 25%) the risk of developing pressure ulcers [104].

18.31 Summary

Nutrition and exercise activity remain the cornerstones of diabetes management but maintaining adequate nutrition is challenging in older people with diabetes,

diabetes complications, and other co-morbidities that compromise nutrition status. The older person must be involved in nutrition decisions and goals wherever possible, and in many cases the family should also be involved, especially if they are documented proxy decision makers. The family can contribute important information to a comprehensive nutrition assessment that can help the healthcare team make nutrition recommendations. Consequently, the nutrition plan must be developed for each individual older person and monitored frequently.

The individual's food preferences and beliefs, cultural background, financial resources, and support system need to be explored and respected. Older people are at risk of nutritional deficiencies and malnutrition, which places them at risk of serious morbidity, compromised independence and quality of life, and is associated with higher mortality rates. These risks can be reduced or prevented with adequate and timely nutrition support.

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CHAPTER 19
Physical exercise management

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KEY MESSAGES

- In older people, diabetes is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass.
- Diabetes mellitus and insulin resistance increase the risk of developing frailty syndrome and may contribute to the increased incidence of falls, institutionalization, and disability.
- Pharmacological and dietary interventions, and exercise interventions, including resistance training, are the cornerstones of diabetes management.
- Apart from the beneficial effects of exercise interventions on glycemic control and the cardiovascular risk factors associated with diabetes, physical exercise is an effective intervention to improve muscle strength, power output, aerobic power, and functional capacity in older patients with diabetes.
- Resistance and endurance training seem to be the most effective exercise interventions to promote overall physical fitness in older patients with diabetes.

19.1 Introduction

Diabetes mellitus is a chronic degenerative endocrine disease that affects millions of individuals, and the complications of this disease progressively affect quality of life and survival [1, 2]. The many complications associated with diabetes include cardiovascular diseases, peripheral neuropathy, retinopathy, chronic renal failure, and impaired mental health [3–5]. In older populations, diabetes is also associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass [6–9]. Indeed, diabetes mellitus and insulin resistance increase the risk for accelerated aging and the development of frailty syndrome [9–11]. The diabetes mellitus disease process may contribute to the increased risk of falls, institutionalization, and disability [12].

Together with pharmacological and dietary interventions, exercise interventions, including resistance training, are the cornerstones of diabetes management [13]. In addition to the beneficial effects of exercise interventions on glycemic control [14] and the cardiovascular risk factors associated with diabetes [15, 16], physical exercise is an effective intervention to improve muscle strength, power output, and aerobic power and functional capacity in older diabetic patients [17–19]. In this regard, combined resistance and endurance training appears to serve as an effective exercise intervention to promote overall physical fitness in older diabetic patients [17]. In addition, in frail older diabetics with severe functional decline, multicomponent exercise programs composed of resistance, endurance, balance, and gait retraining should be employed to increase functional capacity and quality of life, and to avoid falls, institutionalization, and disability [20]. This chapter describes the effects of different exercise interventions on glycemic control in older patients with diabetes. In addition, it provides information regarding the exacerbated reductions in functional capacity in

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those with and without diabetes, and describes the beneficial effects of different exercise interventions on functional capacity.

19.2 The effects of exercise interventions on glycemic control in older people

A large body of evidence indicates that physical exercise exerts beneficial effects on glycemic control in pre-diabetic and diabetic individuals [14, 17, 21]. The mechanisms related to this improvement in glucose metabolism include increased insulin sensitivity, upregulated GLUT4 translocation to the muscle cell membrane independently of the insulin pathway [22], enhanced available glucose storage capacity, thereby facilitating the clearance of glucose from circulation, reduced levels of visceral fat [21], which is the primary cause of insulin resistance, and increased muscle mass, which is the primary tissue involved in glucose metabolism [22].

Although endurance exercise has traditionally been advocated as the most suitable mode of exercise for the treatment of cardiometabolic diseases [23], resistance training has also been consistently shown to effectively reduce the glycemic levels in pre-diabetic and diabetic individuals [14, 19, 21]. In addition, the combination of resistance and endurance training is a more effective exercise intervention to improve neuromuscular and cardiovascular functions than either resistance or endurance training alone. In diabetic patients, this combined training program has the advantage of increasing the total time spent undergoing physical activity, which is also beneficial to these patients. Table 19.1 presents a summary of some studies that investigated the effects of different exercise interventions on glycemic control and functional capacity in older people with type 2 diabetes mellitus.

19.3 The effects of endurance training

Studies on endurance training in older people have demonstrated the beneficial effects of chronic exercise on glycemic control. In a study by Sung *et al.* [24], an interval endurance training program performed three times per week for 24 weeks at an intensity ranging from 55% to 75% of the maximal heart rate (HR_{max}) resulted in a 0.41% decrease in HbA1c levels in older men and women ($n=40$, age 70 years). Using a different training approach, in a study by Nuttamonwarakul *et al.* [25], the cardiometabolic effects of endurance training performed in an aquatic environment at an intensity of 70% of HR_{max}, a duration of 30 min per session, and three sessions per week for 12 weeks were investigated. These authors demonstrated that this training protocol resulted in decreased HbA1c levels (by 1.1%). Therefore, endurance training performed three times per week at a sufficient intensity may reduce HbA1c levels in older people even within a short training period.

Along with the beneficial effects of endurance training on diabetic patients, endurance training has been shown to improve glycemic control in non-diabetic subjects [26, 27]. This finding is especially important because it suggests that physical training can prevent or slow the progression of diabetes in elders.

19.4 The effects of resistance training

Resistance training is also an effective exercise intervention to reduce the glycemic and HbA1c levels in older diabetic patients. In a study by Ibañez *et al.* [21], the effects of a 16-week resistance training program combining heavy and explosive loads were assessed in elderly type 2 diabetic patients. The resistance training program was performed twice weekly and included two exercises for the leg extensor muscles, one exercise for the arm extensor muscle, and from four to five exercises for the main muscle groups of the body. Heavy resistance training was performed using either three or four sets of 10–15 repetitions per set at 50–70% of 1 repetition maximum (RM) during the first 8 weeks followed by between three and five sets of either five or six repetitions per set at 70–80% of 1 RM. During the final 8 weeks, 20% of the training volume of the leg extension and bench press exercises was performed as three or four sets of between six and eight repetitions at 50% of 1 RM in an explosive manner (i.e., as rapidly as possible). The results showed that this training protocol resulted in a marked decrease in the fasting blood glucose levels (7%, $p<0.05$) and a significant improvement in insulin sensitivity by 46% ($p<0.01$) (Figure 19.1). A trend toward a significant decrease in HbA1c levels ($p=0.06$) was observed in this study. Another relevant finding in this study was a significant

Table 19.1 Summary of some studies that investigated the effects of resistance, endurance or combined resistance and endurance training in the elderly with type 2 diabetes.

Author	Subjects	Intervention, period, and weekly frequency	Training volume and intensity	Main results
Castaneda *et al.* (2002) [28]	*n* = 62 Age: 60 ± 1 Men and women	RT 16 weeks Three times per week	Three sets of eight repetitions 60–80% of 1 RM	↓ HbA1c (1.1%) ↑ Whole-body 1 RM (33%) ↓ Systolic blood pressure (10 mmHg)
Ibañez *et al.* (2005) [21]	*n* = 20 Age: 66.6 Men	RT 16 weeks Twice per week	Three to five sets of six to 15 repetitions 50–80% of 1 RM Slow and explosive muscle contractions	↓ Intra-abdominal fat (10.3%) ↑ Leg and arm 1 RM (17–18%) ↑ Insulin sensitivity (46.3%) ↓ Fasting glucose (7%)
Ibañez *et al.* (2008) [18]	*n* = 20 Age: 64.8 (diabetics), 66.6 (control) Men	RT 16 weeks Twice per week	Three to four sets of five to 15 repetitions 50–80% of 1 RM Slow and explosive muscle contractions	↑ Leg 1 RM: control (37%) > diabetics (24%) ↑ Arm 1 RM: control (36%) > diabetics (17%) ↑ Leg and power output (30% of 1 RM) (22–33%), no differences between groups
Dunstan *et al.* (2002) [29]	*n* = 29 Age: 67.6 ± 5 and 66.9 ± 5 Men and women	RT combined with weight-loss program 24 weeks Three times per week	Three sets of eigth to ten repetitions 50–85% of 1 RM	↓ HbA1c (1.2%) ↑ Whole-body 1 RM (33%) ↓ Systolic blood pressure (6.7 mmHg) ↓ Diastolic blood pressure (4.4 mmHg)
Geirsdottir *et al.* (2012) [19]	*n* = 213 Age: 74 ± 1 Men and women	RT 12 weeks Three times per week	Three sets of six to eight repetitions 75–80% of 1 RM	↑ Leg peak torque (15%) ↑ Hand grip (19%) ↑ 6 min walking distance (6 %) ↑ TUG performance (5%) No changes in HbA1c
Brooks *et al.* (2007) [30]	*n* = 62 Age: 66 ± 1 Men and women	RT 16 weeks Three times per week	Three sets of eight repetitions 60–80% of 1 RM	↓ HbA1c (1.1%) ↑ Leg and arm 1 RM (68 and 36%)
Nuttamonwaraku *et al.* 2012 [25]	*n* = 40 Age: 60 ± 1 Men and women	ET 12 weeks Three times per week	30 min at 70% of HR_{max} Water exercises	↓ HbA1c (1.1%) ↑ VO_{2max} (1%)
Simmonds *et al.* (2012) [56]	*n* = 16 Age: 68 ± 4 Women	ET 12 weeks Four times per week	30 min at intensity progressing to anaerobic threshold	↑ VO_2 at anaerobic threshold (10%) No changes in HbA1c
Egger *et al.* (2013) [36]	*n* = 32 Age: 65 ± 8 Men and women	High vs low intensity RT combined with ET 8 weeks	Low-intensity RT: two sets of 25–30 repetitions 40% of 1 RM High-intensity RT: two sets of 10–12 repetitions 70% of 1 RM ET: 60 min at 70% of HR_{max}	↓ Basal glucose in both groups ↑ Arm 1 RM (high-intensity RT > low-intensity RT

(*Continued*)

Table 19.1 (Continued)

Author	Subjects	Intervention, period, and weekly frequency	Training volume and intensity	Main results
Tan *et al.* (2012) [35]	$n=16$ Age: 68±4 Women	CT 12 weeks Three times per week	RT: two sets of 10–12 repetitions 50–70% of 1 RM ET: 30 min at 55–70% of HR_{max}	↓ HbA1c (0.55%)
Kim *et al.* (2014)	$n=52$ Age: 68. 5±1 to 73.2±2.0 Women	CT 12 weeks Three to four times per week	RT: two to three sets per exercise performed as circuit alternation ET: 60–80% of HR reserve	↓ Fat mass (5%) ↓ Total cholesterol (2.2%) No changes in insulin sensitivity

HbA1c, glycated hemoglobin A1c; 1 RM, one maximum repetition (maximal dynamic strength); RT, resistance training; ET, endurance training; CT, combined resistance and endurance training; HR, heart rate; HR_{max}, maximal heart rate; VO_{2max}, maximal oxygen uptake.

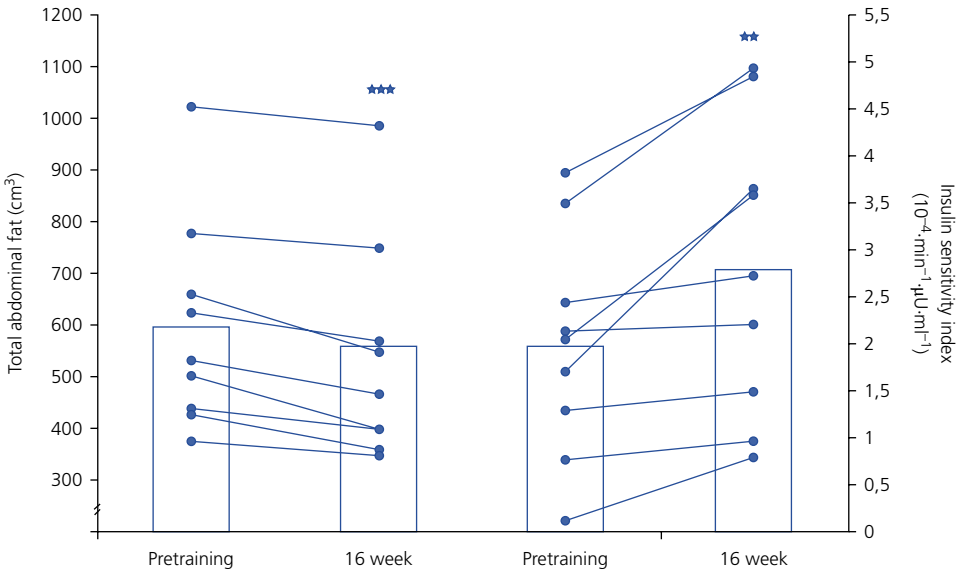

Figure 19.1 Total abdominal fat and insulin sensitivity at pretraining and after a 16-week strength training period for each subject and mean values. $^{**}p<0.01$ and $^{***}p<0.001$ vs the corresponding pretraining value. Adaptated from Ibañez *et al.* [21].

decrease in the amount of intra-abdominal adipose tissue (10.3%, $p<0.01$). Thus, along with its beneficial impact on glycemic control, resistance training that includes heavy and explosive loads can improve the levels of intra-abdominal fat, which is a primary cause of type 2 diabetes.

Other studies investigating the effects of resistance training on glycemic control have reported positive results. In a study by Castaneda *et al.* [28], a resistance training program conducted three times per week for 16 weeks induced a significant reduction in HbA1c levels (by 1.1%, $p<0.05$) in men and women with type 2 diabetes (aged 66±2 years). These authors used a progressive resistance training protocol that began at 60% of 1 RM and progressed to 80% of 1 RM (three sets of eight repetitions). A similar resistance training protocol

was used in the study by Dunstan *et al.* [29], who investigated men and women with type 2 diabetes (aged 67 ± 5 years). These authors showed that progressive resistance training (three sets of eight to ten repetitions beginning at 50–60% of 1 RM and progressing to 75–85% of 1 RM) performed three times per week for 24 weeks induced a significant reduction of 1.2% in HbA1c levels ($p < 0.05$). Similar results were observed by Brooks *et al.* [30], who noted a reduction of 1.2% in HbA1c levels ($p < 0.05$) after 16 weeks of resistance training performed three times per week consisting of three sets of eight repetitions at an intensity ranging from 60 to 80% of 1 RM. In all of these studies, no significant alteration in glycemic control was observed in the control group that did not perform any exercise intervention.

Importantly not all studies investigating the effects of resistance training reported decreases in glycemic or HbA1c levels [19, 31, 32]. For example, in a study by Cheung *et al.* [33], 4 months of home-based resistance training using exercise bands did not promote a beneficial change in glycemic control in aging type 2 diabetic patients (aged 59 ± 8.7 years). This intervention may not have been sufficient to induce metabolic changes in these patients. Other potential causes of the lack of a change in glycemic control after resistance training include uncontrolled diet, an insufficient sample size, and low statistical power to detect significant differences, therefore caution must be taken when prescribing resistance exercise interventions to improve glycemic levels in type 2 diabetic patients.

Along with glycemic control, the effects of exercise on other risk factors associated with diabetes should be taken into consideration. Interestingly, a recent study has shown that even the time of day which the exercise is performed may influence postprandial risk factors. Heden *et al.* [34] have shown than post-dinner resistance exercise reduced postprandial triacylglycerol (92%) (an effect due to reduced VLDL-1) when compared with pre-dinner resistance exercise and no resistance exercise ($p < 0.05$) in obese patients with type 2 diabetes (48.5 ± 11.9). In contrast, both pre- and post-dinner resistance exercise reduced postprandial glucose concentrations with no difference between situations. Therefore, the time to perform exercise in relation to meal times should be considered by healthcare professionals to optimize metabolic benefits in type 2 diabetic patients.

19.5 The effects of combined resistance and endurance training

Few studies have investigated the effects of combined resistance and endurance training on glycemic control in elderly type 2 diabetic patients. In a study by Tan *et al.* [35], a significant reduction in HbA1c levels (by 0.55%) was observed after 24 weeks of combined resistance (three times per week, two sets of 10–12 repetitions at 50–70% of 1 RM) and endurance training (30 min at 55–70% of HR_{max}). Conflicting results were reported by Egger *et al.* [36] and Tessier *et al.* [37], who did not observe any change in HbA1c levels after combined resistance and endurance training for 8 and 16 weeks, respectively. In a study conducted in an aquatic environment, Asa *et al.* [38] observed a significant reduction in HbA1c levels (by 0.7%) after 8 weeks of combined training performed using hydrogymnastic exercises.

Based on these studies, the prescription of combined resistance and endurance training at a sufficient volume and intensity may promote a reduction in glycemic levels in elderly patients. Importantly, according to a meta-analysis conducted on a large age range of type 2 diabetic patients [14], the time spent exercising should be greater than 150 min per week to exert optimal beneficial effects. In this sense, the combination of resistance and endurance training should be recommended because along with enhancing neuromuscular and cardiovascular function, this combined training program increases the total time spent undergoing physical activity, which is also beneficial to type 2 diabetic patients.

19.6 Functional capacity in older diabetic patients

It has been shown that aging patients with type 2 diabetes exhibit greater declines in muscle strength and functional capacity and more rapid loss of muscle mass than normoglycemic controls [6–9]. Indeed, diabetes complications such as peripheral vascular disease and peripheral neuropathy are associated with poor gait ability, impaired balance, and increased risk of falls [39–43].

In a study investigating a large cohort, Park *et al.* [8] followed 1840 elderly adults (73.5 years), 16.6% of whom were type 2 diabetics, for 3 years. These authors

showed that both the diabetics (HbA1c=7.9%) and the non-diabetics (HbA1c=6.0%) experienced a significant loss of initial muscle strength over 3 years but that the older adults with type 2 diabetes lost their knee extensor strength, leg lean mass, and muscle quality (maximal strength per unit of muscle mass in N·m/kg) more rapidly than those without diabetes. In a study by Levinger *et al.* [44], elderly men (54.2±7.4 years) with type 2 diabetes (HbA1c=6.8%) exhibited a lower VO_{2peak} (21.8 vs 25.8 ml/kg/min), maximal strength relative to body mass (chest press+leg press) (3.3 vs 3.7 kg/kg body mass) and performance on physical tasks (i.e., the 15 m rapid walking, timed up-and-go, stair climbing and stair descending tests) (27.2 vs 24.2 s) than men without diabetes (HbA1c=5.5%). In this study, the diabetic individuals also exhibited a more depressed mood and a lower perceived general health. In addition, Leenders *et al.* [7] reported that aging individuals with type 2 diabetes exhibited a greater decline in functional capacity, along with lower-body muscle mass and strength, than normoglycemic subjects.

In another study, Ijzerman *et al.* [45] investigated lower extremity muscle strength in type 2 diabetics with (62 years, HbA1c=7.1%) or without (67 years, HbA1c=7.3%) polyneuropathy and compared these diabetics with healthy individuals (68 years, HbA1c=6.0%). These authors showed that, compared with the healthy controls, the diabetic individuals either with or without polyneuropathy exhibited reduced muscle strength (34–47%), mobility (28%), and quality of life. This study also showed significant associations between muscle strength and mobility and between reduced quality of life and both muscle strength and mobility in diabetics. Similarly, Ko *et al.* [39] observed an association of gait pattern alterations with type 2 diabetes (HbA1c=6.86%) in older adults (70 years) without peripheral neuropathy.

Although aging patients with type 2 diabetes exhibit greater decreases in muscle strength and functional capacity, it has been shown that uncomplicated diabetes does not accelerate age-related sarcopenia [46]. Moreover, the preservation of functional capacity should be specifically addressed in aging diabetic patients because in contrast to other chronic conditions, diabetes care is dependent on the patients' ability to perform self-care tasks [12]. Therefore, in addition to metabolic control, effective strategies are needed to prevent the exacerbated loss of strength and functional capacity in aging diabetic patients because these individuals exhibit an increased risk of developing frailty syndrome, institutionalization, and disability [10–12].

19.7 Resistance training improves muscle strength, power, and functional capacity in older people with diabetes

In addition to its important effect on glycemic control, resistance training is a very important intervention because it counteracts the exacerbated loss of muscle strength and functional capacity observed in elderly patients [18, 19, 28–30]. For example, in study by Brandon *et al.* [47], 24 weeks of resistance training performed at moderate intensity induced increases in muscle strength and mobility in elderly with type 2 diabetes. In general, studies have demonstrated that applying a resistance training intervention consisting of either two or three sets of 8–15 repetitions at an intensity ranging from 50 to 85% of 1 RM performed two or three times per week for between 8 and 24 weeks markedly increases maximal muscle strength in elderly type 2 diabetic patients [18, 19, 28–30].

19.8 High-velocity resistance training in older patients with diabetes

Resistance training programs, especially those including high-velocity muscle actions during the concentric phase, have been demonstrated as effective interventions to improve muscle strength, power output, rate of force development, and functional capacity in elderly subjects [48–51]. In fact, studies have shown that muscle power appears to serve as a more important predictor of functional performance in elderly adults than muscle strength alone [52, 53]. In a study by Ibañez *et al.* [18], elderly diabetic patients who performed a twice weekly progressive resistance training program that included high-velocity muscle actions exhibited significantly improved muscle strength and muscle power output after 16 weeks of training. In a recent study, a 12-week multicomponent exercise program including explosive resistance training significantly increased muscle cross-sectional area, maximal strength, muscle power output, balance, gait, and sit-to-stand

ability, and reduced the incidence of falls of institutionalized frail nonagenarians [54]. Among these subjects, more than 70% suffered from type 2 diabetes as a co-morbidity [54]. Explosive resistance training can therefore serve as an effective intervention to improve neuromuscular and functional outcomes even in elderly individuals exhibiting severe functional decline.

Notably, to improve functional capacity in the elderly, the volume and intensity of exercise interventions must be carefully designed because insufficient training stimuli may result in a lack of benefits to glycemic control and functional capacity in elderly type 2 diabetics. In this sense, although home-based exercise programs may facilitate exercise adherence, this type of intervention may not result in metabolic and functional improvements [33].

19.9 Endurance training and cardiovascular function in older patients with diabetes

Although resistance training is an effective intervention to improve glycemic control and functional capacity in the elderly with type 2 diabetes, its combination with endurance training is the most indicated exercise program because endurance training promotes greater increases in cardiovascular function when compared with resistance training alone [55]. Indeed, studies investigating the effects of endurance training and combined resistance and endurance training have shown marked increases in cardiorespiratory outcomes [25, 56]. Endurance training two to three times a week at intensities around 70% of maximal heart rate should be prescribed in combination with resistance training in order to promote benefits in cardiovascular fitness. As mentioned before, the time spent exercising should be greater than 150 min per week to exert optimal metabolic effects.

19.10 Diabetes, cognitive impairment, and exercise

Another aspect that should be taken into consideration with respect to the benefits of exercise to older diabetic patients is the role of exercise in the prevention of cognitive impairment. Older diabetic patients have been demonstrated to exhibit an increased risk of cognitive impairment and dementia [57]. The factors underlying the association between diabetes and cognitive impairment in the elderly most likely include the influence of cerebrovascular complications of diabetes on brain function and structure, alterations in glucose and insulin levels, and recurrent hypoglycemia, as a history of severe hypoglycemic episodes is associated with an increased risk of late-in-life cognitive deficits and dementia [57]. In this regard, a physically active lifestyle may protect against dementia [58]. Similarly, a decrease in the level of physical activity, such as walking, coincides with a decline in cognitive function [59]. In addition, improvements in cognitive function induced by exercise program performance have been observed in older individuals without dementia [60] or those with mild cognitive impairment [61].

Along with the positive effect of exercise interventions on cognitive function in the elderly, physical training may improve mobility and physical function in elderly patients with dementia [62, 63]. It has been shown that 4 weeks of high-speed resistance training combined with walking, cognitive exercises, and balance exercises improved gait ability, balance, and muscle strength (15–30%), and reduced the incidence of falls in frail patients with dementia after long-term physical restraint during nursing care. In this study, among the several co-morbidities of these patients, the most typical comorbidity was type 2 diabetes [63]. Taken together, these results suggest that exercise may also help to prevent dementia and to improve muscle functional capacity in elderly patients with dementia and that these characteristics may be a consequence of diabetes complications.

19.11 Conclusions: Special considerations when prescribing exercise in older type 2 diabetic patients

In summary, along with pharmacological and dietary interventions, physical training, including resistance and endurance training, represents the cornerstone of diabetes management. In addition to the beneficial effects of exercise interventions on glycemic control and the cardiovascular risk factors associated with diabetes, physical exercise is an effective intervention to improve

neuromuscular and cardiorespiratory function, as well as functional capacity in elderly diabetic patients. Therefore, the combination of resistance and endurance training appears to be the most effective exercise intervention to promote overall physical fitness in elderly diabetic patients.

Based on exercise interventions used in studies which investigated the metabolic and functional effects of exercise in older people with type 2 diabetes, there are some guidelines for exercise interventions in this population:

- Exercise interventions should be composed of at least 150 min of exercise per week, spread over two or three non-consecutive days. However, it has been shown that exercise interventions of more than 150 min per week result in greater effects on glycemic control [14].
- As a part of exercise intervention, resistance training should be performed at least twice weekly, including exercises for all muscle groups. These exercises should be performed using two to three sets per exercise, and repetitions ranging from 8 to 15, with workloads progressing from 50% to 80% of 1 RM. The intensity and volume should be carefully periodized and should increase progressively. Part of the resistance training exercises (especially lower limbs) should be performed as fast as possible (muscle power training) in order to optimize skeletal power output and, consequently, functional capacity. The rest between sets should be 2–3 min.
- Endurance training should be performed three times per week, with each session lasting at least 30 min. The intensity should start between 40% and 50% of HR_{max} and progress to 70–80% of HR_{max}. Endurance training can be performed in either an aquatic environment or on dry land (i.e., walking or cycling).

Of course, we do not underestimate the challenges in introducing these exercise programs to routine clinical diabetes care but health professionals must convince other stakeholders, patients, and families of their importance.

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CHAPTER 20

Medicines, pharmacovigilance, and the importance of undertaking comprehensive assessments and regular medicine reviews

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KEY MESSAGES

- Managing medicines is a comprehensive inter-related process that involves assessing and diagnosing, prescribing, administering and/or medicines self-administration, monitoring outcomes, benefits, and risks, identifying errors and adverse events, and de-prescribing where possible to reduce the medicine burden.
- Medicines are an essential component of the care of older people with diabetes.
- The medicine regimen should be considered as part of the overall management plan and decided *with* the older person, and often their families.
- Polypharmacy is common and associated with medicine-related errors and adverse events, many of which can be prevented.
- Under-prescribing also occurs when medicines are not prescribed when they are indicated and safe.
- Non-medicine options should be used before prescribing medicines when safe and indicated. Non-medicine options can also be combined with medicines.
- Glucose-lowering medicines might be prescribed to manage symptoms, promote comfort, and conserve function: not to achieve "optimal glycemic control".
- Hypoglycemia is the most significant side effect of insulin and some other glucose-lowering medicines, and has significant adverse consequences.
- Individualized medicine education is essential for older people, especially those managing their own medicines, family carers, and health professionals.
- Adequate nutrition and physical activity are still important when medicines are indicated.

20.1 Introduction

This chapter addresses key issues concerning older people and medicine safety. It does not contain prescribing recommendations or medicine algorithms, which can be found elsewhere in the book (Chapters 22–26). The term "medicine" is used in preference to "drug" because it is the preferred term in some countries and, more importantly, because "drug" often refers to illegal drugs. Likewise the term "medicine management" is used to refer to the inter-related processes involved in safe medicine use; except when referring to a specific medicine management activity such as prescribing or administering medicines.

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> "Prescribing in older people is a balance between managing conditions according to disease-based guidelines and addressing the patient's goals while at the same time avoiding medicine-related problems." [1]

Many countries have long life expectancy, therefore the proportion of older people in most countries is increasing. Age is a risk factor for diabetes. Many older people with diabetes have diabetes-related complications and other co-morbidities, and more than 70% of older people are over age 85 [2]. Thus, medicines are an essential component of the care of many older people and are used to manage hyperglycemia, diabetes complications, other co-morbidities, symptoms such as thirst and fatigue, and to enhance comfort and quality of life [3].

However, the more medicines an individual uses the greater the risk of medicine errors, interactions, and adverse events (Box 20.1). Medicine errors are more common than medicine-related adverse events but result in harm less than 1% of the time. However, 25% of adverse medicine events are due to medicine errors [4]. Errors and adverse events occur in the community, in hospitals, and in aged-care homes, and are made by people with diabetes, their family carers, and health professionals. Significantly, medicine administration errors account for 26–30% of total medicine errors in hospital [4].

Aging is associated with changes in glucose homeostasis and in the counter-regulatory response to hypoglycemia as well as other diabetes- and age-related effects on

Box 20.1 Definition of medicine errors, medicine adverse events, adverse medicine reactions, medicine side effects, and medicine interactions.

Medicine errors

Any preventable event that may cause or lead to inappropriate medicine use or patient harm while in the control of the healthcare professional, patient or consumer. Medicine errors can be a consequence of health professional practice, medicines and other healthcare products, guidelines, policies, procedures, and systems, including prescribing; referral, and communication processes, product manufacturing, labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and actual use.

Medicine errors that are identified before harm actually occurs are sometimes called near misses, close calls or potential adverse medicine events. Not all medicine errors lead to adverse events.

Medicine adverse events

A medicine adverse event is an injury resulting from the use of a medicine, including harm caused by the medicine such as an adverse medicine reaction, overdose and harm from using the medicine, such as reducing doses and stopping the medicine. Adverse medicine events can result from medicine errors, but most do not [3].

Adverse medicine reactions

An adverse medicine reaction is a noxious and unintended response to a medicine that occurs at doses that are usually safe for use in humans prescribed prophylaxis, diagnosis or to treat f disease or to modify physiologic function. There is usually a causal link between the medicine and the adverse medicine reaction, which occurs during usual use of the medicine.

Medicine side effects

Side effects are generally expected and known effects of a medicine identified during development and testing of the medicine that are not an intended therapeutic outcome. However, the term "side effect" creates expectations that side effects are normal. In fact, side effects are actually adverse medicine reactions. Significantly, people with diabetes often stop medicines or miss or change doses because of side effects. Hypoglycemia is an example of a very significant adverse event of insulin and some other glucose-lowering medicines that is generally accepted as an expected consequence of these medicines.

Medicine interactions

Medicine interactions are avoidable causes of harm. Harm can occur because of either increased medicine effect causing toxicity or reduced medicine effect that leads to inadequate therapeutic effects. Medicine interactions should be considered when deciding the underlying cause of symptoms because an interaction/s could be the cause/contributing factor and when initiating new medicines, stopping medicines or changes doses and dose regimens. Complementary medicines can interact with conventional medicines. Software checkers for determining medicine interactions are widely available but may not be clinically useful.

renal and liver function and nutritional status that affect medicine safety and medicine choices [5–7]. The long duration of diabetes, hyperglycemia, and glucose variability usually leads to organ and tissue damage, and often requires medicines as well as other management strategies. In addition, increasing age, diabetes complications, and their effects on physical and cognitive functioning, self-care capacity, and self-esteem influence the benefits and risks of individual medicines as well as the combination of medicines, complicate medicines self-management, and increase the self-care burden [8, 9].

Although some age-related changes are relatively predictable, older people with diabetes are not a homogeneous group: they are physically, functionally, mentally, and socially different and have individual beliefs, experiences, capabilities, and needs. Consequently, the medicines regimen must be designed to suit the individual's needs and, where possible, decided in collaboration with the individual (personalized) and/or their family carers [8–10]. Factors that influence medicine decisions include the individual's general health and functional status, their social situation, health and general literacy and numeracy, available support from family and/or the community, and cost. These factors should be included in a comprehensive medicine review that encompasses health and social issues before a medicine is prescribed and at regular intervals. Health status and other factors can change over time, sometimes suddenly; consequently an individual's care needs and medicine regimen can also change.

20.2 Medicine-related vulnerability and older people

It is essential to optimize medicine use in older people [9] because of their increased sensitivity to some medicines due to age-related changes and the significant risk of medicine-related morbidity and mortality (errors and adverse events). As with younger people, medicines are prescribed to cure, slow disease progress, and manage symptoms. Medicines can also reduce the symptom burden, improve quality of life and function, and prevent disability and unnecessary hospitalization. Conversely, medicines also cause significant burden, reduce quality of life, and are a direct cause of hospital admissions. Medicine errors are a common cause of unintentional harm in all settings [11].

Every 6 months two million Australians experience an adverse medicine event. Adverse medicine events lead to 400,000 extra visits to a doctor and 200,000 hospitalizations. Likewise, medicine errors result in approximately 800,000 hospital admissions per year. Approximately 30% of these admissions are people over age 75. Significantly, 60% of medicine histories in hospital contain *at least one* medicine error and previous adverse medicine events and allergies are not recorded in the medical record 75% of the time. More than 50% of medicine errors occur at transitions of care [11].

Although some older people participate in medicine-related research, most research participants are younger than 75 years and are usually in relatively good health and take very few or no medicines. Consequently, a significant proportion of medicine recommendations is extrapolated from research in younger people and/or is based on expert opinion and clinical experience [12, 13]. It is especially difficult to decide how to apply guidelines to frail older people because treatment recommendations are not based on research in this group [14].

Older people have more medicine-related problems than younger people [2] and medicine-related problems in older people are associated with increased costs and hospital admissions, poor outcomes, and longer recovery [15]. Some medicines confer higher risk than others and are designated "high-risk medicines" [16]. Over 60% of medicine-related hospital admissions for adverse events involve warfarin/antiplatelet agents, insulin, and other glucose-lowering medicines alone or in combination: many adverse events are preventable [16]. For example, 27% of adverse medicine-related events in primary care and 42% in aged-care homes are preventable [17, 18].

Medicine errors and adverse events are associated with falls, geriatric syndromes, confusion, delirium, incontinence, and frailty, and contribute to death in older people [16–21]. Common medicine-related errors include prescribing potentially and actually inappropriate medicines and/or prescribing inappropriate doses. Although polypharmacy is common, under-prescribing (not prescribing a medicine when indicated and when it is safe to do so) also occurs and can result in adverse events [22, 23]. Inappropriate prescribing includes not reducing medicine doses when indicated, for example when renal and liver function decline, and not stopping medicines when they do not confer benefits or become unsafe.

Disease- and treatment-related burdens increase with age, therefore it is important make treatment goals and decisions with the older person with diabetes, that is, it is essential to treat the individual not merely their diabetes and other co-morbidities. Significantly, older people with diabetes often value physical functioning, and psychological and social wellbeing more than meeting metabolic targets [24]: focusing on disease processes and treatment targets might not addresses the individual's specific goals or improve their quality of life.

Over-prescribing glucose-lowering medicines or medicine doses can cause hypoglycemia; under-prescribing contributes to hyperglycemia, although the underlying causes of both states are multifactorial, not just a prescribing issue. Hyperglycemia is often accepted as part of aging or attributed to the person not adhering to diet and exercise/activity recommendations, rather than as a result of infection or stress or a potentially preventable and undesirable medicine adverse event, especially in aged-care homes [3, 8, 9, 19].

Hyperglycemia has significant short-term effects on memory and cognition, and causes fluid and electrolyte changes that predispose older people with type 1 diabetes to ketoacidosis and people with type 2 diabetes to hyperosmolar states: both these states have serious consequences, including death. Long-term hyperglycemia damages tissues and organs, and exacerbates other co-morbidities and the aging process [24].

20.3 Polypharmacy

Polypharmacy is common in older people. It is defined as follows:

> "The use of five or more drugs [medicines], including prescribed, over-the-counter, and complementary medicines [concurrently]. It may be a useful prompt for medication review, as it is associated with problems of medication management and suboptimal prescribing." [25].

It can also be defined as older people "taking multiple unnecessary medicines" [21]. The term "polypharmacy" has negative connotations because it is associated with a high risk of medicine errors and adverse events. Diabetes-related polypharmacy usually evolves over time due to the progressive nature of type 2 diabetes and the development and progression of diabetes complications, many of which require medicines for secondary prevention and for treatment. Box 20.2 outlines common causes of polypharmacy.

Because of the multifactorial metabolic derangements that need to be managed, one could argue that polypharmacy could actually be best practice for *some* older people with diabetes. Often more than one of the following types of medicines are required to manage the different metabolic abnormalities: antihypertensives, lipid-lowering and glucose-lowering medicines. However, as the number of medicines increases, the likelihood of potentially and actually inappropriate medicines being prescribed and the risk of inducing a prescribing cascade also increases [25]. Often the risks outweigh the benefits because older people have increased susceptibility to medicine side effects and are more likely to develop medicine toxicity than younger people [25].

Many older people with diabetes take five or more medicines. Taking 4.5 medicines concurrently is associated with increased mortality and falls. Taking 5.5 and 6.5 medicines concurrently is associated with disability and frailty [26]. Significantly, every extra medicine the individual takes increases the risk of falls, disability, and death. The probability of a significant medicine interaction occurring is strongly associated with the number of medicines dispensed [27]. One case-control study found polypharmacy was an independent risk factor for hip fracture [28] but the risk could be due to exposure to particular medicines known to increase falls risk instead of or as well as the number of medicines.

However, it is important to realize that polypharmacy *per se*, is not a clinically useful independent indicator of medicine risk. The characteristics of the individual, each medicine type, dose, the dose intervals, and the total number of medicines prescribed might be better indicators of medicine-related risk [29]. Tools such as the Drug Burden Index [30] can be used to measure exposure to anticholinergics and sedatives, and is a good indicator risk.

Polypharmacy is associated with increased risk of hospitalization or presentations to the emergency department, functional and cognitive impairment, geriatric syndromes, falls, frailty, nutritional deficits, nonadherence, and poor health outcomes. Polypharmacy is also associated with glucose variability and could play a role in oxidative stress and the associated adverse effects on the cardiovascular system [31]. Polypharmacy is also a significant medicine self-care burden for many older

Box 20.2 Factors that contribute to polypharmacy [8, 9, 21, 28, 29].

Related to health professionals

- Prescribers' knowledge and competence to prescribe for older people.
- Age: older physicians are less likely to prescribe new medicines or follow guidelines [65].
- Inadequate communication among health professional carers and with the individual contributes to the prescribing cascade, especially if medicine reconciliation is not undertaken.
- Prescribing cascade where medicines are prescribed to manage symptoms rather than the underlying cause of the symptoms.
- Not stopping unnecessary medicines. Inappropriate/inadequate assessment and clinical monitoring.
- More than one health professional prescribing and managing the individual's medicine regimen.

Related to the person with diabetes

- Older person with diabetes' medicine knowledge, competence, and capacity to advocate for their care, which can affect their capacity to ask questions about medicines and make decisions about self-prescribed medicines.
- The progressive nature of type 2 diabetes, including the development of diabetes complications and other co-morbidities that affect physical, cognitive, and sensory function.
- Older people who self-diagnose and self-medicate use complementary and self-prescribed medicines, or medicines prescribed for a previous illness or for another person.
- Admission to hospital, especially intensive care units, and transfer among care settings.
- Consulting more than one prescriber and having prescriptions filled at more than on pharmacy.

Environment

- Available resources and staff.
- Health professional medicine knowledge and competence.

people with diabetes and is associated with increased healthcare costs [26]. High medicine burden is positively associated with increased risk of functional decline in community-dwelling older people [25] and increased risk of falls in aged-care homes [32].

Medicine-related decisions are difficult when polypharmacy, co-morbidities, and frailty overlap, and when there is uncertainty about the benefits and risks of individual medicines and the combination of medicines for the individual. They can lead to health professional clinical inertia and delay decisions about stopping, starting or changing medicines and other treatment [3]. Medicine-prescribing indications can alert clinicians to the prescribing risks and benefits, but the clinician must assess the individual's risk profile and discuss their risk with the individual. Likewise, it is essential to ask about complementary medicines (herbal medicines and supplements) and other self-prescribed non-prescription medicines when considering the medicine regimen because these medicines are associated with particular risks and contribute to polypharmacy [11, 33]. People with diabetes frequently use complementary medicines for a range of reasons [33, 34].

Older people living in aged-care homes are some of the most vulnerable members of the population. Forty per cent of older people in aged-care homes and 20% of community-dwelling older people are prescribed at least one inappropriate medicine [18, 19]. The focus in aged-care homes is often on administering medicines, which is a challenging and time-consuming task for staff, especially given the staffing and resource issues in many aged-care homes and the frequent interruptions that occur during medicine administration rounds.

Other key medicine-related activities are often suboptimal in aged-care homes, for example not timing glucose-lowering medicine doses to be given with meals and not timing blood glucose tests to suit the action profile of the glucose-lowering medicine, not testing blood glucose at all, or testing too infrequently to determine a blood glucose pattern. Despite the debate about the value of people with type 2 diabetes testing their blood glucose, it remains the most useful indicator of

prevailing blood glucose levels and the emerging blood glucose pattern, and is helpful in deciding whether glucose-lowering medicines are needed and the required doses and dose frequency.

20.4 Pharmacovigilance

The World Health Organization (WHO) defined "pharmacovigilance" as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related [medicine] problem" [35]. The WHO established a program for international drug monitoring after the thalidomide disaster that occurred in 1961. WHO promotes pharmacovigilance at the country level in collaboration with the WHO Collaborating Centre for International Drug Monitoring, Uppsala. The aims of the pharmacovigilance initiatives are to enhance medicine-related patient care and safety, and to support medicine public health programs and initiatives by providing reliable, balanced information to help health professionals and policy makers assess the risk–benefit profile of medicines.

Despite the plethora of research and information about medicine safety, managing medicines is complex in older people and often "it is impossible to separate the chance of good from the risk of ill" [36]. Many health professionals often focus on prescribing and administering medicines and the older person's non-adherence to medicines, yet as indicated, *managing* medicines is a broader concept. Many experts believe adverse medicine events are under-reported [37] due to differing perceptions about how an adverse medicine event is defined and the fact that age-related changes can be mistaken for an adverse medicine event [37].

Medicines for older people are divided into potentially and actually inappropriate categories: Beers criteria [38]; STOPP [39], START [40]. Inappropriate prescribing for older people is a significant cause of adverse medicine events, yet potentially inappropriate medicines are frequently prescribed for older people, often as first-line treatment, even when there is good evidence that they lead to suboptimal outcomes [39, 41–43].

However, it is important to acknowledge that many potentially inappropriate medicines are prescribed appropriately for the individual's health needs when the medicines were first prescribed. Problems occur when they are not stopped when the acute health problem resolves and they are no longer needed. Stopping some medicines could prevent many unintended errors and adverse events. Usually, the risks associated with potentially inappropriate medicines outweigh the benefits for older people, especially when other, safer options are available, for example using cognitive behavior therapy if the person is not cognitively impaired or acupuncture to manage pain. These issues highlight the importance of frequently reviewing the older person's medicine regimen before prescribing or stopping a medicine when health status fluctuates and for proactive medicine reconciliation.

As indicated, medicine-related adverse events often lead to hospital admissions. Many potentially inappropriate medicines and actually inappropriate medicines are prescribed during the hospital stay, often in intensive care units [44, 45]. Older people who are discharged from intensive care units often leave on polypharmacy. They may have several transitions to other hospital wards during an admission and are often transferred to other services such as rehabilitation and aged-care homes. Consequently, they are at high risk of medicine adverse events after discharge [44, 45].

Morandi *et al.* [42, 43] found 85% of older people who were discharged from intensive care to other wards eventually left hospital on one or more potentially inappropriate medicines and >50% were discharged with one or more actually inappropriate medicine. Opioids, anticholinergics, and antidepressants are commonly prescribed potentially inappropriate medicines in older people: they cause or contribute to confusion, delirium, cognitive impairment, falls, and other risks. The doses and dose frequencies of these medicines are likely to be inappropriate at discharge [42–44].

Ninety per cent of people over age 65 use at least one medicine and 50% use more than five medicines, more than any other age group [43]. The author conducted a point prevalence survey in the hospital where she works as part of a larger study and found older people with diabetes were using an average of seven medicines in multiple doses throughout the day: range 1–17 [44]. In addition, many used between one and five complementary medicines, especially vitamin and mineral supplements [33, 44].

Table 20.1 depicts some of the age- and diabetes-related changes that affect medicine safety and the risks

Table 20.1 Factors that can influence glucose-lowering medicine risks and benefits in older people with diabetes (adapted from the Australian Medicines Handbook [5] and Dunning and Sinclair [6]).

Factor	Prescribing considerations
Polypharmacy	Medicine–medicine interactions Risk of prescribing potentially inappropriate medicines and actually inappropriate medicines Whether multiple prescribers are involved Likelihood of presentation to emergency department/admission to hospital Complex medicine self-management burden, which increases the risk of non-adherence Driving safety could be compromised
Age- and diabetes-related effects on the gastrointestinal system Autonomic gastric neuropathy Changed appetite, dysphagia Malabsorption: food and medicines Reduced gastric acid production Reduced saliva production Nausea and vomiting Nutritional deficits	Reduced appetite Some medicines increase the risk of hypoglycemia and further reduce the already compromised ability to mount a counter-regulatory response to hypoglycemia Weight loss may not be appropriate in overweight older people because of the associated loss of muscle mass and strength, and the risk of sarcopenia and associated falls risk Some oral glucose-lowering medicines stimulate appetite, which may be positive for some older people Nausea, vomiting, and bloating may impair medicine absorption from the gut or can be a side effect of many medicines and/or illnesses Using medicines that delay or increase absorption of medicines or nutrients from the gut when the individual has existing gastrointestinal co-morbidities, for example antacids and metformin reduce vitamin B_{12} absorption in some individuals, antibiotics and phenytoin reduce folic acid absorption, corticosteroids, thiazide diuretics, and some antipsychotic medicines contribute to hyperglycemia Hyperglycemia, protein deficits, and weight loss lead to low serum protein and body water, which affects medicine binding, consequently more free medicines are in circulation Weight gain and increased deposition of body fat leads to increased storage of fat-soluble medicines and delayed elimination, resulting in unpredictable action profiles Difficulty swallowing some medicines, which can lead to non-adherence or inappropriate medicine crushing Difficulty distinguishing hyperglycemia-related dry mouth from medicine side effects Increased risk of some medicines damaging tooth enamel High-fiber diet can increase gut transit time and reduce medicine absorption Enteral and supplementary feeds may be needed if the individual has swallowing difficulties or is frail The medicine dose form may need to be changed, for example large tablets that are difficult to swallow and medicines that should not be crushed because they irritate the gut and their action profile will be changed People over 70 years often have nutritional deficits such as low protein stores (muscle mass) and vitamin D, B_{12}, C, and E, calcium, and magnesium deficits
Reduced renal function Increased renal threshold for glucose	Compromised renal function leads to reduced medicine clearance and more circulating medicine in the blood Renal anemia Risk of kidney damage with some medicines, including complementary medicines and investigative procedures involving radio contrast media Microalbuminuria is associated with dementia, which inhibits medicine self-care and decision-making and increases hypoglycemia risk Macroalbuminurea predicts hypoglycemia HbA1c is less reliable in the presence of renal disease and anemia Dialysis might be needed in end-stage renal disease Glucose urine tests are unreliable Urine glucose testing is not appropriate to detect hypoglycemia Driving safety could be compromised
Liver damage	Reduced metabolism of some medicines Monitor liver function

(*Continued*)

Table 20.1 (Continued)

Factor	Prescribing considerations
Reduced cardiac output and reduced peripheral blood flow	Delayed medicine transport to target tissues, therefore delayed action and effectiveness Higher medicine levels in the circulation and longer duration of action Fluid retention, which affects medicine uptake in the tissues
Silent myocardial infarct and sudden death	Hypoglycemia precipitates cardiac events such as myocardial infarction and arrhythmias, which are secondary to autonomic activation of the counter-regulatory response to low blood glucose and result in hemodynamic changes, vasoconstriction, intravenous coagulability, and viscosity Driving safety could be compromised
Inadequate and inappropriate support from others	Isolation, people who have limited social contact and support are more likely to become depressed and non-adherent to the management plan, particularly medicines Reduced intake Driving safety could be compromised

and benefits that need to be considered when making medicine choices. Some medicines can also compromise driving safety. Educating the individual and their family about such risks is an important aspect of medicine management. Driving risk applies to all motorized vehicles, including wheel chairs, ride-on lawn movers, and tractors.

20.5 Common medicine-related issues in older people

Many medicines commonly prescribed for older people should be used with caution or not prescribed [4, 9–11, 20, 42–45]. Key issues include the following aspects of management.

20.5.1 Initiating new medicines

New medicines can lead to a prescribing cascade when a medicine is prescribed to treat a side effect of another medicine [46]. Thinking "is it an adverse event/side effect" before prescribing medicines for any new condition or problem and using non-medicine treatment where possible helps prevent the prescribing cascade. New medicines can increase the risk of medicine interactions and the severity of adverse events associated with current medicines. The risk factors for a prescribing cascade are the same as those for medicine adverse events, as already discussed.

The risk of an adverse event is highest soon after starting a new medicine. Approximately 90% of adverse events occur within 4 months of commencing the medicine. Of these 75% occur in the first month [46]. Thus, extra-vigilant monitoring is required when commencing new medicines. Antihypertensives, sedatives, opioids, antibiotics, antinauseants, anti-epileptics, and NSAIDs are commonly associated with prescribing cascade-related adverse events.

It is possible that glucose-lowering medicine prescribing algorithms could contribute a prescribing cascade. Glucose-lowering medicine recommendations are primarily based on physiology. However, the patient's perspective and health status, cost benefit, and risk benefit as well as prescribing information need to be considered [47]. The prescribing cascade can be reduced by undertaking risk screening, stopping medicines before prescribing new medicines if possible, undertaking regular comprehensive medicine reviews, educating health professionals, older people, and their families, and closely monitoring the outcomes [3, 43, 44]. Significantly, a prescribing cascade is more likely when multiple prescribers are involved and the medicine list is not current.

20.5.2 De-prescribing

De-prescribing refers to tapering medicine doses, withdrawing or discontinuing unnecessary medicines [38]. Decisions to withhold medicine doses in aged-care facilities and at home can be difficult for health professionals, older people and families. Having *individualized* hypoglycemia and sick day-care plans and policies for fasting and investigations can help decision-making. It is sometimes difficult to determine whether functional decline or medicine discontinuation syndromes will

Box 20.3 Hypoglycemia risk factors in older people [6, 7, 47–49] (see also Chapter 24).

- Age.
- Prescribed glucose-lowering medicines, especially some sulfonylureas and/or insulin.
- Long duration of diabetes, which is associated with progressive changes in the counter-regulatory response to hypoglycemia, in particular diminished secretion of glucagon and growth hormone, which contributes to hypoglycemia unawareness.
- "Tight" blood glucose control.
- Renal and liver disease.
- Nutritional deficits, which compromise ability to respond to the counter-regulatory response to low blood glucose.
- Cognitive impairment and dementia, which make it difficult for the individual and health professionals to recognize hypoglycemia.
- Multiple diabetes complications and other co-morbidities that cause functional deficits and compromise diabetes self-care.
- Most current hypoglycemia education programs and policies are not tailored for older people, for example the focus on adrenergic hypoglycemia symptoms such as sweating and trembling when neuroglypenic symptoms such as confusion and behavior change are more common in older people and contribute to hypoglycemic unawareness.
- Recent hypoglycemia.
- Inappropriate treatment of hyperglycemia with top-up doses of insulin.
- History of severe hypoglycemia.

occur if medicines are stopped and families might feel care is inadequate, which can put stress on health professionals, especially in end of life situations (see Chapter 36).

Scot *et al.* [48] recommended using a stepwise approach to stopping medicines and highlighted the importance of asking relevant questions to detect non-adherence. Issues to consider before stopping a medicine/s include medicine toxicity, life expectancy, whether the person is approaching the terminal end-of-life stage, and their care and life goal.

20.5.3 Hypoglycemia

Hypoglycemia is the most common medicine adverse event in older people with type 2 diabetes [49]. It is more common and serious than hyperglycemia, but is still a common underlying cause of hospital admissions in people over age 75 [49]. Hypoglycemia has significant psychological and social consequences and can affect self-confidence and mood.

Hypoglycemia is a significant risk associated with insulin and some sulfonylureas, especially long-acting preparations [3, 4, 9, 38, 40, 48, 49]. Older people with type 1 and type 2 diabetes are vulnerable to hypoglycemia, which may account for one in five hospital admissions in older people with diabetes aged 80 years and older [50]. Prescriptions of long-acting sulfonylureas such as Glibenclamide may have been inappropriate in a large number of people with dementia and/or renal failure. Glibenclamide is no longer used in many countries.

The causes of hypoglycemia are usually multifactorial (see Box 20.3 and Chapter 27). Hypoglycemia can have serious adverse consequences and can precipitate life-threatening events such as stroke and myocardial infarction [51]. Myocardial infarction might be "silent" and not diagnosed. Other hypoglycemia-associated cardiac events include acute cardiac failure and ventricular arrhythmias, and longer hospital stay and increased costs in older people with type 2 diabetes [52]. In addition, hypoglycemia is associated with short-term changes in delayed and working memory [53], which affect problem-solving, decision-making and self-care capacity, and with dementia in the longer term [54, 55].

It is often difficult to detect hypoglycemia in older people because neuroglycopenic symptoms are more common than the usual list of adrenergic symptoms described in most existing information about hypoglycemia used to educate people with diabetes and health professionals. Neuroglycopenic symptoms can be mistaken for confusion/delirium and treatment can be delayed or not occur. The changed symptomology occurs because the counter-regulatory response to hypoglycemia declines over time. The glucagon response

is virtually absent in many older people [52] and contributes to hypoglycemia unawareness, which increases the risk of severe hypoglycemia. In addition, glucose stores might not be adequate to respond to the counter-regulatory hormones in older malnourished people. Macroalbuminuria predicts severe hypoglycemia [56].

20.5.4 Under- or malnutrition

Nutritional deficiencies contribute to low glucose stores in muscle and liver, and affect fat and protein stores (see Chapter 20). Low serum albumin can affect the action of protein-bound medicines. Older people are more sensitive to medicines that affect the neurologic and cardiovascular systems than younger people. The half-life of medicines can be significantly increased in older people due to underlying disease processes, including renal and liver disease, and influence medicines choices, doses, and dose intervals [3, 27].

20.5.5 Renal function

Changes in renal function and chronic kidney disease are common in older people with diabetes and are a predictive risk factor for medicine-related adverse events, especially hypoglycemia and falls [3, 8, 9]. Age-related changes also occur and may mean some medicines are contraindicated or should be used with caution and renal function monitored.

20.6 Medicine adherence

Many medicines used to treat diabetes, its complications, and other co-morbidities are regarded as high-risk medicines because they are associated with significant side effects and because of their pharmacodynamics and pharmocokinetics, for example insulin and anticoagulants [17]. High-risk medicines can cause catastrophic harm when used in error. However, they can also cause significant harm when they are used appropriately if their effects are not monitored closely and when the dose and/or dose regimen is not safe for the individual.

Adherence to treatment, including dietary advice, exercise/activity when using medicine, is an issue in all age groups. Only approximately 50% in the general population take the full course of medicines [57]. Non-adherence is costly and is associated with increased hospital admissions, lower medicine efficacy, increased morbidity and mortality, and functional decline [19]. There is a very large body of information about patient-related non-adherence but very few studies examine the effect of health professional behavior, prescribing habits, and their medicine beliefs on patient adherence.

However, "adherence" is a highly complex issue that involves:

- acceptance: the individual choses to use the medicine to improve or maintain their health
- adherence: the degree to which the individual actually follows the medicine regimen and adopts appropriate medicine self-management behavior
- persistence: continuing to use the medicine for the required time. Many medicines prescribed for older people will be required for the rest of their lives, which can be a long time to expect them to persist [45].

Some of the factors that affect adherence include:

- cognitive function
- physical function
- whether the individual is involved in making medicine choices
- patient and health professional attitudes, beliefs, and previous experience
- culture
- availability of medicines
- social issues such as cost and capacity to have prescriptions filled
- quality and personal relevance of the medicines education the individual receives [59, 60].

Various measures are used to monitor adherence, including:

- medicine counts, usually in research settings
- prescription refills
- self-report
- medicine and other diaries, such as blood glucose monitoring records
- health professional reports, which often differ from the patient's perspective
- reports from others such as families, which can also differ from the patient report
- electronic devices such as metered-dose inhalers
- blood and urine tests such as HbA1c, lipids, and blood pressure [45, 58].

Improving medicine adherence is important as poor adherence has a greater cumulative effect over time than short-term poor adherence [57]. Strategies such as choosing the medicine choices and dose regimen with the individual, simplifying the dose schedule, and providing appropriate personalized education can help,

but sometimes older people still need help from families or health professionals to use their medicines safely. A combination of strategies is more likely to be effective.

20.12 Antipsychotic, antihypertensive, and lipid- and glucose-lowering medicines

Antipsychotic medicines are often prescribed to manage behavior problems associated with dementia but have adverse consequences. Some contribute to hyperglycemia.

Antihypertensive medicines are discussed in Chapter 25. Some antihypertensives contribute to postural hypotension and can lead to falls [58]. However, not all antihypertensives cause postural hypotension or increase falls risk. Sometimes first-dose effects occur and resolve over time. The newer slow onset antihypertensives are less likely to cause postural hypotension and the associated falls risk [59]. Other factors such as age, sudden changes in position, and heat can precipitate postural hypotension. General prescribing recommendations are to "start low and go slow." Some lipid-lowering agents are contraindicated if the person has liver disease. Liver function declines with age, therefore monitoring liver function is an important aspect of managing some medicines. Lipid-lowering medicines are discussed in Chapter 26.

Initiating or intensifying medicine treatment in older people with type 2 diabetes who are not using glucose-lowering medicines or insulin in hospital was not associated with unplanned readmissions to hospital in a recent study [60]. Those with higher HbA1c had reduced likelihood of early readmission. Not surprisingly, those with higher Charlson Comorbidity Index scores had longer length of stay and were more likely to be discharged home with nursing support.

Sliding insulin scales/top-up insulin doses are often used to manage transient hyperglycemia, especially in aged-care facilities [41, 42]. Sliding insulin scales/top-up doses do not address the underlying factors that cause hyperglycemia, such as urinary tract and foot infections, diet, stress, pain, and depression. Top-up insulin doses might reduce the blood glucose on a temporary basis but hyperglycemia often reoccurs unless the underlying cause is identified and treated.

Hyperglycemia can lead to hyperosmolar states, confusion, delirium, falls, reduced quality of life, and symptomatic discomfort [7, 8, 41]. Sliding insulin scales/top-up insulin doses are not recommended for routine hyperglycemia management [41]. Sliding insulin scales may be indicated in acute illnesses such as ketoacidosis and hyperosmolar states in acute care situations when the insulin is usually administered intravenously (Chapter 19).

20.13 Infrequent blood glucose testing

Health professionals debate the value of blood glucose testing in type 2 diabetes, especially in aged-care homes. When blood glucose testing is performed, the testing regimen is not related to meal times or to glucose-lowering medicine action profiles, especially peak action times for insulin. However, blood glucose testing is the most effective currently available method of determining ambient blood glucose and the emerging blood glucose pattern and, consequently, glucose-lowering medicine types, doses, and dose frequency. *One could argue that not testing blood glucose could lead to significant safety issues*.

20.14 Frailty and cognitive changes

These conditions have profound effects on adherence to treatment and the ability to achieve safe, appropriate care targets (see Chapter 18). Understanding the concept of frailty could help health professionals prescribe appropriately for older people. Incorporating frailty measures such as the Clinical Frailty Scale and the Frailty Index into future clinical studies that explore medicine effects and pharmacokinetics will be important to improve safe medicine use and guide medicine doses appropriate for frail older people in the future [12].

20.15 Falls risk

Falls are a significant risk associated with 50% of the medicines most commonly prescribed for older people. These medicine types include most of the medicines that affect the central nervous system,

glucose-lowering medicines, and opioids [60]. Falls are discussed in detail in Chapter 34.

20.16 Health professionals, people with diabetes, and/or family medicine-related beliefs and attitudes

Medicine-related and cultural beliefs and attitudes about medicines influence the medicine behavior of older people with diabetes and health professionals' prescribing habits. Both groups often do not consider medicine adverse events as possible causes of symptoms, which can lead to a prescribing cascade where a medicine is prescribed to treat the symptom. However, symptoms are often non-specific and atypical in older people, which makes it difficult to identify and then treat the cause [61, 62], or medicines are stopped before the full course is completed and 40% are not taken as directed.

Older people's medicine beliefs are multifactorial and develop over their lifetime. Older people tend to consider costs, likelihood of side effects from personal experience and the experience of others, and the effects on their daily life activities when managing their medicines, including adhering to the recommended regimen. Some people are concerned about the stigma associated with some medicines, including insulin, and the overall burden of the medicine regimen [63, 64]. People are more likely to take medicines if they believe they will be beneficial.

20.17 Strategies that can help reduce medicine-related adverse events

Medicine-related education for health professionals is essential. It is difficult to identify health professional-related factors that lead to inappropriate prescribing. Some factors include inadequate communication among multiple prescribers, knowledge deficits, and ageist attitudes, for example older physician are less likely to follow guidelines or prescribe new medicines for various reasons [65]. It is likely these traits also occur in other health professional disciplines.

Hamilton [66] proposed five rules that can help health professionals improve medicine safety:

1 Determine existing interactions as part of the differential diagnosis.
2 Know the pharmacological effects of any medicines prescribed and the individual older person's physiology to help determine the benefits of any potential pharmacological interactions.
3 Know that medicines with a narrow therapeutic index are high risk.
4 Some medicines that affect the liver P450 enzyme system induce other medicines and stopping or starting such medicines can cause interactions.
5 Health professionals improve their own knowledge, competence, and medicines management systems to improve continuity of care, especially at care transitions.

Another rule is to take care in hospital and aged-care homes with medicines such as insulin where doses can vary and errors are common, for example wrong dose, omitted doses, delayed doses or incorrect insulin type. Most insulin errors occur during insulin administration [17].

20.18 The five rights of administering medicines

Nurses are familiar with the five rights mantra of medicine administration:

- right patient
- right medicine
- right dose
- right route
- right time [67].

Despite the widespread use of the five rights, administration errors still account for 26–32% of the total medicine-related errors and such errors are not intercepted by recent technological advances in medicine safety. The five rights are broad goals rather than outcomes. They do not offer guidance about how to achieve the goals and do not ensure medicine safety [67]. Several other authors have suggested including various other rights, such as right formulation, right reason, and right documentation.

Other strategies used to reduce medicine risks include reading back to verifying telephone medicine prescription orders, double-checking medicines with a colleague, avoiding non-approved abbreviations, TALLMAN letters, medicine alerts, and ensuring a zero is placed before decimal points in medicine doses [68].

Many medicine errors in hospital and aged-care homes are caused by nurses being interrupted during medicine rounds and other environmental factors such as noise and poor lighting. One or more of these factors can affect more than one medicine and medicine calculations [67]. The more interruptions there are during the medicine round the greater the number and severity of errors [69]. An average of 11% of each medicine round is spent dealing with interruptions.

Kreckle [70] suggested wearing some form of identifiable clothing such as a tabard to reduce interruptions and the strategy has been identified in several institutions around the world with varying success. For example, Scott *et al.* undertook a 5-week audit in Aberdeen Royal Infirmary in Scotland in acute medical, surgical, and specialist cardiology and urology wards [70]. Nurses wore red tabards embroidered front and back with "Drug round in progress. Please do not disturb." Interruptions slightly reduced from six to five and there was a slight reduction in interruptions during the 5 weeks. Tabards are used in other parts of the world with varying success.

20.19 Medicine reviews and risk assessments

Regular comprehensive medicine reviews and medicine reconciliation programs are essential, especially when several doctors prescribe medicines for the same person [3]. A medicine review must include information about the individual's medical and medication history, including previous adverse events and allergies, health status, physical, cognitive and sensory functional status, social circumstances and available support, especially if the individual lives in the community.

Home medicine reviews can elicit important information about the social factors that affect medicine self-management. The information can be used to determine the individual's risk of medicine-related adverse events and to plan care to reduce the risk [8]. Involving families in case conferences can help identify problems and find solutions [68, 69].

Medicine reviews should aim to identify key related risks such as potentially and actually inappropriate medicines, duplicate prescriptions, complementary medicines, over-the-counter (self-prescribed) medicine use, risk of hypoglycemia and hyperglycemia, other adverse events, falls, pain, and self-care capacity. It is essential to maintain up-to-date medicine histories and medicine lists, and communicate any changes to everybody involved in the individual's care, the individual, and his or her family carers in a timely manner and using appropriate language and design/format for written material.

Liver and renal function should be monitored regularly and checked before commencing some medicines such as metformin. Both decline with increasing age, for example most people over age 60 have some changes in liver and renal function [5, 51]. Doses of medicines such as ACE, NSAIDs and Cox-2 inhibitors might need to be reduced or the medicines stopped because they contribute to declining renal function. Some glucose-lowering medicines such as metformin should be used with caution when renal function declines; although the actual level of renal function when metformin should be ceased is still debated (Chapters 10 and 23).

The medicine regimen should be reviewed or re-prescribed every time a medicine is started or stopped, an adverse event occurs or health status changes. An admission to hospital is an ideal time to undertake a medicines review and assess an individual's understanding of their medicines and their medicine self-management behaviors and capacity. Admission and discharge between wards/units and between care settings are high-risk times for adverse events: medicine reconciliation should occur at every transition [18, 19, 40, 44, 45].

Primary care doctors, diabetes educators, and other carers can play an important role in medicine reviews. They should be informed about the outcome of any medicine review and changes to the medicine regimen and care plan, and the reason for the changes that occur in hospital because they can help the older person understand the changes and monitor the outcomes. Likewise, primary care doctors should clearly communicate any changes they make to the individual's medicine and care plan to other health professionals.

Quality use of medicines (QUM) [76/8] is a key aspect of Australia's medicine policy and has been adapted for use in other countries, for example Canada. QUM encompasses the entire medicine pathway (from bench to bedside), regulatory processes, and labeling, and advocates using non-medicine options when they are safe and evidence-based. It is a useful framework for using the information from comprehensive assessments

to make decisions about the medicine regimen, doses, and dose frequency.

The Institute of Safe Medicine Practice [70] identified 10 key elements that have the most effect on medicine safety:

1 patient information
2 medicine information
3 good communication
4 medicine language, labeling, and packaging
5 the way medicine devices are acquired, used, and maintained
6 environmental factors
7 health professional education and competency
8 patient education
9 medicine quality processes and risk management.

Several decision-support tools are available to help health professionals manage medicines for/with older people. These include:

- BEERS criteria [38, 41]
- STOPP [39]
- START [40]
- Australian Inappropriate Medication Use and Prescribing Indicators Tool [5]
- guidelines such as the National Institute of Clinical Excellence (NICE), the National Prescribing Service (NPS) [3], the McKellar Guidelines [8], and the International Federation Global Guideline for Managing Older People with Type 2 Diabetes [71]
- various medicine adverse event risk assessment tools such as the National Prescribing Service Medicines Risk Screen [72] and the Glucose Lowering Medicine-related Adverse Event Risk Assessment Tool [8]
- high-risk medicine alerts [17].

STOPP helps identity potentially avoidable adverse events [39] but BEERs and STOPP identify different adverse event rates. For example, in 871 patients in hospital BEERs indicated 58.4% were at risk of being prescribed a potentially inappropriate medicine, STOPP identified 75%, and using both tools together identified 78%. Interestingly, the potentially inappropriate medicines identified using STOPP were significantly associated with adverse events (OR 2.36, 95% CI 1.10–5.46) and reduced physical functioning (OR 2.60, 95% CL 1.10–3.64). BEERs showed a positive trend in these parameters but there was no significant association with these variables using BEERS or using both tools together [73]. The authors suggested using both sets of criteria is likely to identify more episodes of potentially inappropriate prescribing that may or may not lead to adverse events [73].

The differences in performance between the two tools could relate to the heterogenetic nature of the criteria in both tools: only 25 of the 99 criteria in BEERs are the same or similar to STOPP. Likewise, 36 of 65 STOPP criteria are not included in BEERs. START is likely to predict all adverse events and reduction in function [73]. BEERs was developed in the USA and STOPP is used more frequently in Europe and increasingly in Australia. These tools were developed to aid medicine prescribing decisions, not replace reasoned clinical decision-making based on a comprehensive assessment. In addition, some decision-support aids, including the widely cited BEERS criteria, are not appropriate for every country because the medicines on the list are not commonly used or are not available in some countries.

It is essential to prescribe medicines appropriate for the individual's clinical context when using these decision tools and alerts. As indicated, making decisions in collaboration with people with diabetes, their families, and the multidisciplinary team facilitates appropriate individualized prescribing. As stated, repeatedly, involving the individual in such decisions enhances medicines self-care.

These tools focus on high-risk medicines but many adverse events are due to commonly prescribed and self-prescribed medicines that are not on lists such as BEERs and STOPP. Miller *et al.* [74] reported that 11.6% of people had at least one adverse event in the preceding 6 months, most of which were mild to moderate, 11.8% were severe, and 5.4% required a hospital admission as a result of using 13 commonly prescribed medicines not on BEERS or other lists.

As indicated, people with diabetes frequently use complementary medicines, some of which have particular risks such as renal damage and hypoglycemia when used alone or with conventional medicines [33, 34]. Complementary medicines are not included in BEERs, STOPP or START or other frequently used tools. It is essential to ask people with diabetes or their families whether they use complementary medicines and other complementary medicines, and monitor their use as part of the individual's medicine regimen and care plan.

I make no apologies for repeating the following information yet again because it is often overlooked in busy clinical settings. It is essential to involve the older person and/or their family carers in medicine and other

care decisions. Involving older people in care planning and decisions improves medicine adherence and concordance, and, importantly, many older people want to be involved in decisions about stopping and starting and changing doses [45, 64]. Older people place great importance on maintaining function and independence and managing their medicines, and want to be involved in care decisions [23] but they often feel they are not involved as much as they want, especially in aged-care homes.

Older people have often lived with their diabetes for many years and are experts in their diabetes, consequently many are functionally independent. Personalized medicine education is more effective than standard education that does not take account of the individual's personal risk factors, literacy level, and other needs and/or the needs of family carers and is more likely to improve adherence. There are many reputable online sources of medicine information as well as phone apps that can help people manage their diabetes and medicines safely.

It is important to identify individual factors that can lead to medicine non-adherence, such as polypharmacy, misinterpreting medicine side effects, not understanding the directions for use, medicine beliefs and attitudes, costs, and access. Tools to assess medicine adherence include the following:

- The Medication Adherence Questionnaire (MAQ), also called the Morisky Scale [75], identifies barriers to adherence but not self-efficacy. The MAQ is often used in research and for hypertension, dyslipidemia, and diabetes. It only has modest validity (Cronbach's alpha 0.61).
- The Medicine Adherence Rating Scale (MARS) is specific to psychiatric populations [76] (alpha 0.75).
- The Brief Medication Questionnaire (BMQ) [77] is used for diabetes depression and has an overall accuracy rating of 95% but no Cronbach's alpha statistic.
- The Self-efficacy for Appropriate Medicine Use Scale (SEAMS) [78] has an alpha of 0.89, indicating high internal validity.
- The Hills-Bone Compliance Scale [79] was designed for use in black populations in the USA (Cronbach's alpha 0.65).

The alpha scores of these tools show that most only have modest internal reliability, which needs to be considered when deciding whether to use them in clinical care and research. The BMQ and SEAMS assess barriers to self-efficacy but are difficult to score.

Strategies such as cues to remember when to take medicines and providing the individual with medicine lists and information in a language, reading level, and format older people can understand and that takes account of the way older people learn, remember, and retrieve information is essential. It is best to involve them at an early stage when the content and design of the information are being decided. Most of the commonly available pharmaceutical company medicine information and material, such as consumer medicines information, are at a very high reading levels and are not designed to suit people with sensory deficits such as vision deficits. They also often contain the information health professionals feel they need rather than what the individual actually needs or wants.

Older people with diabetes receive information about commonly used medicines from various sources, including pharmaceutical companies and national medicine organizations, most of which is distributed by a variety of health professionals who may explain the information differently or not discuss it all. A great deal of medicines information concerns medicine side effects, interactions, and other risks that cause emotional responses in individuals with diabetes and lead to a range of behaviors such as fear, anxiety, stopping the medicine, seeking information on the Internet and/or from family and friends, and undertaking their own risk–benefit analysis based on their emotional response [80]. People feel more comfortable only being told about the very common side effects of medicines and knowledge of rare and very rare side effects only increases their fear and non-adherence [80].

Medicine education must be unbiased, clear, and written in understandable language (suited to the target audience). Several medicines organizations, for example the European Commission [81] and the Australian National Prescribing Service [3], have developed criteria that medicines information should comply with, which includes factors such as readability, design and layout with respect to color contrast between text and background, font size and font type, and white space. Medicines information should be used as part of quality medicines education that is personalized for the individual, for example helping them decide their risk of hypoglycemia and strategies to minimize the risk.

However, a great deal of medicines information does not conform to these criteria and is not suitable for

people with vision problems. The information is also not personalized for the individual during education sessions. In addition, many illustrations used, such as disembodied eyes, kidneys, and hearts, affect people's willingness to take medicines [27]. Word choices also have an effect. For example, some older people do not want to take "drugs" because they associate the word with illegal drugs and wrongdoing.

20.20 Medicine dose aids

Reminder packaging such as medicine dose aids, such as compartmentalized plastic boxes, blister and bubble packs, and sachet systems, are widely used in aged-care homes and for community-dwelling older people receiving support to stay at home. A recent Cochrane review using pooled data from several studies but none that included older people found dose administration aids only increased the percentage of medicines taken by a modest degree (mean difference 11%, 95% CI) [82]. NICE in the UK indicated the evidence for the benefits of using dose aid was not strong enough to recommend widespread use [83].

Australian guidelines recommend medicines are kept in their original packaging unless a dose administration aid is indicated for specific problems [84]. The guidelines recommended using practical strategies such as simplifying the medicine regimen and using reminder alerts, calendars, and phone apps before using dose aids. Dose aids are most effective when the older person is motivated and willing to take their medicines, has the physical and mental capacity to do so, and understands how to use the medicine aid safely [85]. Errors can occur when the dose aids are packed, and ideally the medicine names should be checked before they are taken, but that is very difficult when they are not in their usual packaging.

Some older people like dose aids because they reduce the stress associated with managing medicines and simplify the process. Others prefer to keep their medicines in the original packaging and feel that gives them more control over their medicines, others find dose aids difficult to use, and some people find them demeaning, paternalistic, and a threat to their independence [85]. It is important to realize older people often develop their own version of a medicine "dose aid," which can increase medicine risks.

20.21 Technology and apps

Many phone apps available to assist people to use their medicines safely. Such apps can help people monitor their diabetes, for example the GlooKo Log book, MyNet Diabetes Tracker, and aLife Diabetes Companion, or help with nutrition, such as My Glucose Buddy and Carb Counting with Lenny. MediSafe is a medina app that has many helpful functions. Insulin dose calculators and medicine list/record-keeping apps are also available and some of the latter can be directly linked to the pharmacy or doctor.

A recently launched app (Vida) enables people to consult with their health professionals from their smartphone at a small weekly cost. The app includes reminders to take medicines and the individual can enable their health professionals and family to access their information. The benefits for older people are unclear but the cost may be prohibitive for some people. Such technology might not suit all older people, depending on their physical and mental capabilities, interest, and the design of the app.

Computerized physician order entry (COPE) encompasses a variety of systems for prescribing medicines that range from systems that only provide a list of medicines for prescribers to choose from to systems that have various levels of inbuilt decision support, for example the facility to check for interactions and recent laboratory investigation results. Some have medicine alert facilities that flag medicine risks such as allergies.

There is still debate in the literature on the effectiveness of COPE. A recent systematic review of 25 studies found medicine error was significantly reduced in 23 studies by 13–99%, potential adverse events were reduced by 35–98% in six of nine studies, and four of seven studies showed adverse events were reduced by 35–98% [86]. It is difficult to interpret these data because the studies varied in quality. Studies that compared electronic prescribing to handwritten prescriptions using medical chart audits to detect errors suggest electronic prescribing is associated with fewer risks [86]. Electronic systems are particularly useful if there are effective links among the person with diabetes, the pharmacy, and the prescribers. However, they rely on technical knowledge and competency.

It is not clear whether automated alerts for doctors actually improve prescribing. Many ignore the alert, some feel they lack clinical relevance and do not incorporate any clinical context, and some develop "alert

fatigue" [88]. One potential useful intervention is a computerized electronic surveillance dashboard to identify high-risk or potentially inappropriate medicine prescribing, and medicines with high anticholinergic score combined with proactive pharmacist review [87]. This system flags individuals prescribed at least one potentially inappropriate medicine or high anticholinergic score. One hundred and seventy nine of 797 individuals (22%) admitted in a 3-week period and 485 patient-medicine pairs were reviewed by a pharmacist. The medical records of 71 patients which included 139 patient–medicine pairs were also reviewed manually within the system. Twenty-two patients receiving 40 inappropriate medicine prescriptions warranted an intervention. The intervention was delivered by text message, personal communication, or telephone. Clinicians enacted 31 of the 40 recommendations (78%).

This pharmacist review was associated with improved prescribing and a trend towards improved satisfaction, fewer presentations to the emergency department, and fewer deaths. The study showed the system was technically feasible but it did not monitor clinical outcomes. It is also expensive and difficult to implement in many places [88].

20.22 Medicine environment

It is important to ensure that the environment in which medicines are managed has the relevant infrastructure to actively support patient safety, generally, and medicines in particular. The infrastructure in hospitals and aged-care homes should include ready access to medicine guidelines and polices to support safe medicine practice and good communication practices, for example automated alerts to medicine allergies, hypoglycemia risk, complementary medicine use, and prescribed high-risk medicines. Currently, hypoglycemia risk and complementary medicine use are not standard medicine alerts. Medicine lists for people with diabetes can be helpful if they are kept current and communicated among health professionals caring for the individual, especially prescribers. Usually a combination of methods is more effective than a single strategy.

It is important that health professionals and older people with diabetes and their families report medicine-related adverse events, including those that involve complementary medicines. Reporting adverse events is an important aspect of medicine safety. Adverse event reports contribute to the body of information that enables the safety, quality, and effectiveness of medicines to be monitored and is an essential aspect of post-market surveillance. Most countries have a medicine adverse event reporting process. The following information should be included on an adverse event report:

- the contact details of the person making the report
- patient identifiers
- a comprehensive, clear, and factual description of the adverse event
- details of the medicine believed to have caused the event.

20.23 Summary

Hippocrates' statement "first do harm," is as true today as it was when he first said it. Diabetes is a chronic, incurable, and prevalent disease in older people due to age-related and other changes in glucose homeostasis that can lead to diabetes-related complications and other co-morbidities, which can affect physical, social, sensory, and cognitive functioning, medicine safety, risk–benefit, and medicine self-care capacity.

Polypharmacy is common and represents a significant medicine and self-care burden, as well as risk of medicine-related adverse events and inappropriate prescribing. Some medicines used to treat diabetes, such as insulin, sulfonylureas, warfarin, and antiplatelet agents, are known as high-risk medicines because of their association with adverse events.

Managing medicines is a complex process that requires particular knowledge, skills, and strategies to proactively identify risks and plan care to reduce risks. Following evidence-based recommendations/guidelines can help but there is not a lot of randomized controlled evidence to support recommendations, especially in frail older people.

Comprehensive assessment and monitoring medicine choices can improve medicines prescribing and safety. Likewise, using decision-support tools such as BEERs criteria, and STOPP and START criteria can reduce medicine-related adverse events. It is important to understand the older person's medicine beliefs, attitudes, and their life and care goals and targets, to involve the individual and/or family in medicine decisions, and to personalize medicines education and the medicine regimen.

Table 20.2 Examples of some commonly prescribed medicines that can increase or lower blood glucose.

Medicines that increase blood glucose (diabetogenic)	Medicines that lower blood glucose, excluding glucose-lowering medicines
Diabetogenic medicines increase blood glucose in older people at risk of diabetes but without a diagnosis. Some dibetogenic medicines are potentially or actually inappropriate. They may be appropriate treatment for the individual's illness at the time. The individual and their carers should be informed about the potential effect on blood glucose when medicines that increase blood glucose are commenced and what to do if the blood glucose is affected. Blood glucose monitoring is useful to detect changes early. Medicines should be used at the lowest effective dose for the shorted possible time and in the least diabetogenic dose form. It is important to manage the hyperglycemia to reduce the associated risks such as dehydration, delirium, falls, incontinence, and candida infections. Examples include: • corticosteroids, especially long-acting oral preparations • antipsychotics, especially atypical antipsychotics • sympathomimetics such as adrenaline and salbutamol • thyroid and growth hormones • thiazide diuretics • some antihypertensive medicines such as atenolol, carvedilol, and metoprolol • some herbal medicines such as chrysanthemum extract, honey bee pollen, and tamarind. (Note: people generally use these medicines to treat intercurrent illnesses not to manage blood glucose. Significantly, most of the information is based-on single case reports, which do not provide the botanical names of the herbs in the medicine.)	Determine the individual's hypoglycemia risk before commencing medicines that can increase the hypoglycemia risk or mask hypoglycemia symptoms if used with glucose-lowering medicines. The individual and their carers should be educated about the possibility that the medicine could reduce blood glucose when such medicines are commenced and about what to do if the blood glucose does go low. Blood glucose monitoring is useful to detect changes early. Examples include: • sulfonamides • salicylates • warfarin • MAO inhibitors • tuberculostatics • tramadol [5, 89] • herbal medicines that can lower the blood glucose, for example aloe, ginseng, *Momordica charantia* (bitter melon), *Trigonella foenum graecum* (fenugreek) and *Opuntia* species (prickly pear), especially if they are combined with conventional glucose-lowering medicines (Note: there is some reasonable quality research to support the glucose-lowering effects of these medicines) • alcohol. Note: Some medicines can cause either hypo- or hyperglycemia, for example magnesium salicylate, lithium, lanreotide.

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CHAPTER 21

Glucose-lowering drugs

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KEY MESSAGES

- The aims of treating type 2 diabetes in older people include relief of osmotic symptoms and, where clinically indicated, prevention of long-term microvascular and macrovascular complications.
- In the majority of patients with type 2 diabetes lifestyle measures, that is, diet and exercise, must be supplemented with appropriate pharmacological therapy in order to attain glycemic targets that are appropriate for the individual.
- All patients must have risk–benefit analysis for the use of glucose-lowering drugs the individual.
- Cautions and contraindications pertaining to each agent must always be observed to minimize the risk of unwanted effects, particularly hypoglycemia.
- Sufficient residual pancreatic β-cell function is necessary for most of these drugs to exert their maximal glucose-lowering effects. Combinations of drugs from different agents, for example insulin sensitizers + insulin secretagogues, are often required as endogenous insulin production wanes. Ultimately, insulin replacement therapy is required by many patients after failure to maintain glycemic control with two or three oral agents.
- Biguanides and sulfonylureas have well-established places in treatment algorithms. Metformin, which improves insulin sensitivity without increasing bodyweight gain or serious hypoglycemia, is the most used oral glucose-lowering agent. Severe renal impairment is the main contraindication. Gastrointestinal symptoms may limit the maximal dose.
- Sulfonylureas stimulate insulin secretion; weight gain and hypoglycemia are important adverse effects. Meglitinides are shorter-acting insulin secretagogues that largely share the unwanted effects of sulfonylureas.
- α-glucosidase inhibitors slow the digestion of complex carbohydrates, delaying glucose absorption and reducing postprandial hyperglycemia.
- Thiazolidinediones increase insulin sensitivity by stimulating the peroxisome proliferator-activated receptor-γ (PPAR-γ), altering the expression of a range of genes that control glucose and lipid metabolism. These agents do not cause hypoglycemia but can cause weight gain, fluid retention, cardiac failure, and skeletal fractures. Regulatory action to withdraw (in Europe) or restrict the use of (in the USA) roglitazone was taken in 2010 in response to safety concerns.
- Two new classes of oral glucose-lowering drugs have become available during the last decade. Inhibitors of the enzyme dipeptidyl peptidase-IV (DPP-4) raise plasma concentrations of insulinotropic incretin hormones and enhancing glucose-dependent insulin release. DPP-4 inhibitors, which also reduce inappropriate glucagon secretion, do not cause weight gain or serious hypoglycemia when used as monotherapy.
- Sodium-glucose co-transporter-2 (SGLT2) inhibitors promote urinary glucose excretion, lowering blood glucose and promoting weight loss.
- Other novel classes of glucose-lowering agents are in development. It is essential that their efficacy and safety is rigorously evaluated in clinical trials.

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21.1 Introduction

The pharmacological management of diabetes in older people is recognized to be complex and challenging [1]. After decades of reliance on biguanides and sulfonylureas, novel classes of oral drugs for type 2 diabetes, most notably the thiazolidinediones, started to be introduced into clinical practice in the 1990s [2]. This progress has continued with dipeptidyl peptidase (DPP-4) inhibitors and, most recently, sodium-glucose co-transporter-2 (SGLT2) inhibitors being positioned within treatment algorithms alongside more established agents. These new classes avoid some of the adverse effects and limitations of older drugs such as biguanides and sulfonylureas. Their availability also offers greater opportunity for individualizing therapy [3]. However, no diabetes drugs are devoid of unwanted effects. By definition, clinical experience with newer drugs is limited and their long-term efficacy and safety have yet to be fully quantified [4, 5].

A few guiding principles are warranted at the outset. The management of type 2 diabetes centers on relieving acute osmotic symptoms and, in the longer term, preventing or retarding the development of microvascular and macrovascular complications. More often than not, lifestyle measures have to be supplemented with pharmacological therapy in pursuit of glycemic goals. In general, oral glucose-lowering agents are used first as long as major insulin deficiency is not present. Sufficient residual pancreatic β-cell function is necessary for several classes of oral drugs to exert their glucose-lowering effects, a notable exception being the SGLT2 inhibitors [6]. Clinicians should be aware of a subgroup of patients with latent autoimmune diabetes of adulthood (LADA), which can be confirmed by measuring islet antibodies such as those directed against glutamic acid decarboxylase 65 (GAD65) [7]. These individuals, who are typically but not always non-obese, progress to insulin therapy faster than those with more typical type 2 diabetes. Combinations of drugs from different agents, for example insulin sensitizers + insulin secretagogues, are often required as endogenous insulin production wanes. Ultimately, insulin replacement therapy is required by many patients after failure to maintain glycemic control even with two or three oral agents. Various options are available when transitioning to insulin and often one, less commonly more than one, oral agent is continued in combination with insulin. Numerous clinical guidelines for initiating, monitoring, escalating, and adding oral glucose-lowering drugs are available. The 2011 European Diabetes Working Party for Older People clinical guidelines for type 2 diabetes mellitus [8] and the International Diabetes Federation (IDF) report on managing older people with type 2 diabetes [9] offer evidence-based recommendations for the use of glucose-lowering drugs in older people. The IDF report acknowledges that all glucose-lowering agents can be used safely for treatment of type 2 diabetes in older people. Most agents are equally efficacious when used as monotherapy and will lower HbA1c by approximately 1% (11 mmol/mol) with α-glucosidase and DPP-4 inhibitors have a little lower efficacy, lowering HbA1c by 0.5–0.7% (6–8 mmol/mol), respectively [9].

Balancing the risk–benefit profile of glucose-lowering drugs, and setting and maintaining glycemic targets appropriate to the individual have become major tenets of modern diabetes therapy. Special care must be taken in older patients, who often have co-morbidities such as renal or hepatic impairment, cardiovascular disease, cognitive impairment or frailty [10, 11]. Use of glucose-lowering drugs in patients with type 2 diabetes must balance the glucose-lowering efficacy, side-effect profiles, anticipation of additional benefits, cost, and other practical aspects of care, such as dosing schedule and requirements for glucose monitoring [12]. Wherever possible the patient and/or his or her carers should participate in a shared decision-making process regarding both the intensiveness of blood glucose control and which medications are to be selected. While shared medical decisions may help to improve adherence to the agreed regimen, the evidence base specific to this age group remains limited.

Coronary artery disease and stroke are the leading causes of premature mortality in type 2 diabetes. While some classes of glucose-lowering drugs improve lipid profiles and reduce blood pressure, with the possible exception of metformin, no diabetes drugs have been shown to reduce the risk of macrovascular disease; this remains something of a "holy grail" in diabetes pharmacotherapy. Accordingly, glucose-lowering therapy must be complemented by lifestyle and, where appropriate, pharmacological measures directed at reducing the risk of atherothrombotic complications: However, the positive effects of these risk factors cannot be assumed to translate into better clinical outcomes in the long term.

This lesson has been brought home by the controversy that led to the demise of rosiglitazone in Europe [13].

The chapter is organized as follows. First, drugs with effects regarded primarily as enhancing or mimicking the actions of insulin are considered; this group includes metformin and thiazolidinediones. This is followed by a review of drugs that increase insulin secretion, that is, sulfonylureas, meglitinides, and DPP-4 inhibitors (the latter also having effects on glucagon secretion). Then the α-glucosidase inhibitors are considered followed by the latest class of oral glucose-lowering agents, the SGLT2 inhibitors (see Table 21.1 for pharmacological actions). Drugs from other classes that are not universally available and are used infrequently, that is, colesevalam and bromocriptine-QR (quick release), are also briefly discussed. The chapter concludes by considering some oral glucose-lowering drugs currently in clinical development.

21.2 Insulin-sensitizing drugs

21.2.1 Biguanides

Metformin (dimethylbiguanide) is the preferred agent first-line therapy if lifestyle modifications alone are not adequate to achieve glycemic goals, in both younger and older adults with diabetes. Its low potential for hypoglycemia and low cost combined with high efficacy are favorable features [9]. Biguanides have been in clinical use since the 1950s but metformin was not approved in the USA until 1994. Another formerly widely used member of the biguanide class, phenformin (phenethylbiguanide), was associated with an increased cardiovascular mortality rate compared to insulin in the University Group Diabetes Program [14]. The drug was withdrawn from the UK and many other countries in the late 1970s because of its association with lactic acidosis, a metabolic emergency which carries a high case fatality rate [15, 16]. Buformin (1-butylbiguanide) is still available in some parts of the world.

Metformin is the most extensively used oral agent for type 2 diabetes. Metformin has approximately 50–60% bioavailability and is absorbed mainly in the small intestine. It binds appreciably to plasma proteins. The maximum plasma concentration is observed approximately 2 h after oral dosing. Metformin combines a negligible risk of hypoglycemia or weight gain together with low cost and decades of experience in clinical use. Metformin has long been regarded as the drug of choice for overweight or obese patients because it does not does cause weight gain and may aid modest weight reduction [17, 18]. Metformin can be used in combination with any other class of oral glucose-lowering agent, as well as with insulin therapy. Metformin is commonly continued when insulin therapy is initiated for patients with type 2 diabetes in whom glycemic targets cannot be attained using oral glucose-lowering agents [19]. In an analysis of 23 clinical trials, when compared with insulin alone, the combination of metformin and insulin resulted in lower HbA1c levels, less weight gain, and lower insulin doses, albeit with evidence suggestive of a higher risk of severe hypoglycemia [20].

21.2.1.1 Mechanism of action

The predominant action of metformin is to reduce the inappropriately elevated levels of hepatic glucose production that drive fasting hyperglycemia in type 2 diabetes [21]. This is achieved predominantly through decreased gluconeogenesis [22]. Metformin also reduces hepatic glycogenolysis. Insulin-stimulated glucose uptake via GLUT4 receptors and glycogen formation in skeletal muscle are also enhanced [23]. Reduced fatty acid oxidation may also contribute to metformin-induced improvements in intermediary metabolism [24]. Stimulation of adenosine 5′-monophosphate-activated protein kinase (AMPK) is implicated in the effects of metformin on lipid metabolism, which include suppression of lipogenic genes [25]. Metformin improves aspects of insulin action, including fasting hepatic insulin sensitivity and glucose clearance [21, 26]. Recent data suggest that part of the effect of metformin on fasting glucose levels may be attributable to decreased glucagon-dependent glucose output from hepatocytes [27]. At the cellular level, metformin improves insulin signaling thereby activating the cellular energy regulating enzyme AMPK [28]. In addition to direct effects in hepatocytes a recently reported duodenal AMPK-dependent neuronal-mediated gut–brain–liver pathway may contribute to the reduction in hepatic glucose production induced by metformin [29]. Blood glucose is lowered effectively without the risk of hypoglycemia at therapeutic dosages. In practice, hypoglycemia only becomes an issue during metformin therapy when the drug is used in combination with another glucose-lowering agent, for example a sulfonylurea, or insulin, which itself has the intrinsic capacity to

Table 21.1 Classes of glucose-lowering agents (with insulin as a comparator) and associated characteristics.

Drug or drug class	Efficacy	Risk of hypoglycemia	Effect on weight	Risk of major side effects	Costs
Metformin	High	Low	Neutral or loss	Gastrointestinal effects (frequent), lactic acidosis (rare)	Low
DPP-4 inhibitor	Intermediate	Low	Neutral	Rare	High
GLP-1 receptor	High	Low	Loss	Gastrointestinal effects: nausea, vomiting	High
Insulin (usually basal)	Highest	High	Gain	Hypoglycemia	Variable
Sulfonylurea	High	Moderate	Gain	Hypoglycemia	Low
Thiazolidinedione	High	Low	Gain	Edema, heart failure, bone fracture	High
SGLT2 inhibitor	High	Low	Loss (full safety profile still emerging)	Risk appears low	High

DPP-4, dipeptidyl peptidase; GLP-1, glucagon-like peptide 1; SGLT2, sodium glucose cotransporter 2.
Adapted from Fonseca VA. The Role of SGLT-2 Inhibitors in the Management of Type 2 Diabetes Mellitus. Projects in Knowledge, 2014.

cause hypoglycemia. While insulin-independent effects on glucose metabolism have been reported, experimental studies have shown that metformin requires the presence of insulin in order to exert its acute antihyperglycemic effects [30].

More recently, a putative role for metformin as an anticancer agent has emerged [31, 32]. Metformin inhibits mitochondrial complex I (NADH dehydrogenase) activity and cellular respiration in tumor cells [33]. Metformin also activates AMPK which, in addition to its role in regulating cellular energy balance, has emerged as a possible metabolic tumor suppressor [34]. Reductions in plasma insulin concentrations, which reflect insulin-sensitizing properties, are another postulated anticancer action of metformin [32]. Meta-analyses have shown that metformin is associated with reduced cancer incidence and mortality [35]. The reductions in risk appear to be of modest magnitude, with heterogeneity between reported studies [36]. Clinical trials are underway to determine if these observations apply to non-diabetic populations and to specific organs.

21.2.1.2 Efficacy

Optimally titrated metformin monotherapy can generally be expected to reduce fasting plasma glucose by approximately 2–4 mmol/l and to decrease HbA1c by 1–2% after a few months. However, as with all glucose-lowering drugs observed responses are variable between patients. Factors such as the pretreatment HbA1c and the degree of insulin deficiency in the individual contribute to this heterogeneity. No particular class of oral glucose-lowering drugs can be regarded as being consistently more efficacious than the alternatives [37]. While progress has been made in clarifying the pharmacogenetics of metformin and other glucose-lowering drugs this knowledge has not been translated into clinical practice [38, 39].

21.2.1.3 Effects on cardiovascular risk factors and clinical outcomes

The position that metformin enjoys as foundation pharmacotherapy also reflects its performance in the UK Prospective Diabetes Study (UKPDS). The mean age of the patients studied in UKPDS 34 was 53 years and male body mass index was 31.6 kg/m^2. As was the case for sulfonylureas and insulin, metformin provided long-term protection against the microvascular complications of diabetes. However, in contrast to the aforementioned comparators, metformin reduced the incidence of macrovascular events compared with conventional, that is, diet, therapy [40]. Uniquely among the classes of glucose-lowering drugs studied in UKPDS, metformin therapy, compared with conventional treatment, was associated with risk reductions of 32% (95% confidence interval (CI) 13–47, $p=0.002$) for any diabetes-related endpoint, 42% for diabetes-related death (95% CI 9–63,

$p=0.017$), and 36% for all-cause mortality (95% CI 9–55, $p=0.011$) [40]. Metformin also reduced the risk of myocardial infarction (relative risk reduction 39%, $p=0.01$) as a secondary endpoint. All of these benefits persisted in the 10-year observational follow-up study that followed the UKPDS [41].

Of note, the clinical benefits of metformin in UKPDS 34 were not attributable to more effective glycemic control compared to sulfonylureas or insulin, an observation that pointed to additional cardiometabolic effects beyond glucose-lowering Based on the results of animal and human studies metformin is credited with vasculoprotective effects [42]. Postulated mechanisms by which metformin may reduce the risk of vascular events include countering elevated levels of triglycerides, plasminogen activator inhibitor-1 (PAI-1), factor VII, and C-reactive protein [43]. However, the contribution of these actions to the beneficial effects of cardioprotective effects of metformin in UKDPS remains uncertain [44]. Detracting somewhat from the main results reported in UKPDS 34 are results from some clinical studies, including data generated by the UKPDS itself, that have suggested that combination therapy using metformin with a sulfonylurea may have detrimental consequences for cardiovascular disease and/or survival [40, 45]. In the UKPDS, 537 non-overweight and overweight patients, mean age 59 years, who were already on maximum sulfonylurea therapy but had raised fasting plasma glucose were randomized to continuing sulfonylurea therapy alone ($n=269$) or to the addition of metformin ($n=268$). Early addition of metformin in sulfonylurea-treated patients was associated with an increased risk of diabetes-related death (96% increased risk; 95% CI 2–275, $p=0.039$) compared with continued sulfonylurea alone [40]. However, an analysis of the possible association of death from diabetes-related causes with the concurrent therapy of diabetes in 4416 patients in UKPDS did not show an increased risk in diabetes-related death in patients treated with a combination of sulfonylurea and metformin (risk reduction 5%; CI –33 to 32, $p=0.78$) [40]. In a meta-analysis of observational studies combination therapy of metformin and sulfonylurea significantly increased the relative risk of cardiovascular hospitalization or mortality (fatal and nonfatal events) irrespective of the reference group (diet therapy, metformin monotherapy, or sulfonylurea monotherapy) used [46]. However, there were no statistically significant effects of combination therapy of sulfonylurea and metformin on cardiovascular mortality or all-cause mortality [46].

21.2.1.4 Cautions and contraindications

The controversy concerning use of metformin in patients with renal impairment reflects concerns about the most feared, if uncommon, adverse event – lactic acidosis – resulting from inhibition of the mitochondrial respiratory chain. The dose should be reduced if the estimated glomerular filtration rate (eGFR) is 30–60 ml/min, and the drug should not be used if eGFR is <30 ml/min [47, 48]. Since metformin is rapidly cleared by the kidney (approximately 90% within the first 12 h) any degree of renal dysfunction carries the risk of an increase in the plasma level of metformin [22]. Diabetes is the leading cause of end-stage renal disease (ESRD), accounting for approximately 50% of cases in the developed world [49]. Moreover, with aging populations and rising diabetes rates diabetic nephropathy is increasingly becoming a disease of older people [50]. Metformin-associated lactic acidosis is a rare complication of treatment which has mainly occurred in patients with serious renal insufficiency or other contraindications to the use of the drug [51]. However, the intrinsic risk of lactic acidosis with metformin is estimated to be 10–20 times lower than that for phenformin [52]. This reflects factors such as differences in routes of metabolism and effects on tissue lactate production of the two drugs [32, 52]. An analysis of prospective comparative trials and from observational cohort studies concluded that there is no evidence that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other glucose-lowering drugs [53]. A recent systematic review reported that plasma levels of metformin generally remain within the therapeutic range and circulating lactate concentrations are not substantially increased when used in patients with mild to moderate chronic kidney disease (estimated glomerular filtration rate 30–60 ml/min per 1.73 m^2) [54]. The overall incidence of lactic acidosis in metformin-treated patients varied across studies from approximately 3 per 100,000 person-years to 10 per 100,000 person-years, rates indistinguishable from the background rate in the overall population with diabetes [54]. However, no randomized controlled trials have been conducted to test the safety of metformin in patients with impaired kidney function. Guidelines offering thresholds of renal impairment at which

metformin should be avoided have generally not been tested in prospective clinical trials [55]. It has been suggested that current guidelines on the use of metformin in the presence of renal impairment are too strict and deny many patients the potential benefits of the drug [56, 57]. In a 2015 update of a position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) the expert writing group observed that current cut-off points for renal safety in the USA (contraindicated if serum creatinine ≥133 µmol/l (≥1.5 mg/dl) in men or 124 µmol/l (1.4 mg/dl) in women), which were based on pharmacokinetic data, may be overly restrictive [12]. The IDF guideline on managing older people with type 2 diabetes recommends use of eGFR as a more accurate indicator of renal function than serum creatinine in this age group [9]. Calculation of eGFR in older individuals using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) formulas have a similar performance [58] while the Cockroft Gault formula tends to underestimate eGFR.

While it could be argued that the data concerning the safety of metformin in patients with renal impairment remain less than conclusive, Inzucchi and colleagues have offered an alternative dosing strategy that cautiously opens the use of the drug to more patients [54]. Suggested doses range from 2550 mg for patients with an eGFR of ≥90 ml/min/1.73 m^2 down to 1000 mg for patients with an eGFR of 30 to <45 ml/min/1.73 m^2, and a recommendation to avoid use in those with an eGFR below 30 ml/min/1.73 m^2 [54]. The authors stress the need for careful monitoring of renal function. One clinical scenario in which acute decreases in GFR can lead to metformin accumulation is contrast-induced nephropathy in patients undergoing imaging procedures. However, inconsistences between published guidelines on avoiding contrast-induced lactic acidosis have been reported [59]. The use of metformin in patients with cardiac or respiratory insufficiency and during major intercurrent illnesses such as severe infection, dehydration, recent myocardial infarction, or shock should be avoided. All of these conditions predispose to tissue hypoxia and hyperlactatemia. Liver disease, alcohol abuse, or a history of metabolic acidosis are regarded as additional contraindications [22]. Long-term treatment with metformin can reduce intestinal absorption of vitamin B_{12} [60, 61].

21.2.1.5 Tolerability

Tolerability issues are well recognized with metformin and limit the use of the drug in clinical practice [52]. These are mainly related to the gastrointestinal tract and include a metallic taste in the mouth, abdominal discomfort, and diarrhea. Gastrointestinal side effects can be minimized by starting with a low dose of metformin, for example 500 mg daily with a main meal, and gradually increasing the dose over the following few weeks. If troublesome gastrointestinal symptoms develop a lower dose of metformin may be tolerated by some patients. In clinical trials, approximately 5–10% of patients find that gastrointestinal symptoms preclude long-term therapy. A trial of extended-release metformin, which is associated with a lower incidence of gastrointestinal side effects than the standard formulation, may be useful [62].

21.2.2 Thiazolidinediones

The thiazolidinediones were introduced into clinical practice at the end of the 20th century, just after the UKPDS reported on the effects of glucose-lowering pharmacotherapy based on sulfonylureas, metformin, insulin, and acarbose [63, 64]. The arrival of the thiazolidinediones was widely regarded as a welcome means of countering insulin resistance in skeletal muscle [64]. The latter defect in insulin action, present in the great majority of patients with type 2 diabetes, had been identified as a logical therapeutic target [65].

The first thiazolidionedione to be marketed – troglitazone – was subsequently withdrawn because of severe idiosyncratic hepatotoxicity that resulted in the deaths of a number of patients and the need for liver transplantation in others (see below) [66]. Two other thiazolidinediones – rosiglitazone [67] and pioglitazone [68] – became available shortly after troglitazone. While neither of these drugs was associated with adverse hepatic effects, rosiglitazone was withdrawn from the European market in 2010 and use of the drug was restricted in the USA the same year [13]. As detailed below, these actions were the culmination of a controversy that revolved around concerns that rosiglitazone was associated with an increased risk of myocardial ischemic events. Other safety and tolerability concerns require careful consideration, especially in older patients [9]. However in selected older people these agents may still have a useful role due to their efficacy, low risk of hypoglycemia, and once-daily dosing.

21.2.2.1 Mechanism of action

Whole-body insulin sensitivity is improved by thiazolidinediones via stimulation of a widely distributed nuclear receptor known as peroxisome proliferator-activated receptor (PPAR)-γ [69]. Following binding to the receptor, a heterodimer molecule that contains the binding site is activated. The activated complex binds to the response elements of specific genes that regulate molecules with effects on insulin action and lipid metabolism. This promotes adipocyte differentiation and lipogenesis mainly in subcutaneous fat depots [70]. Improvements in insulin-mediated glucose uptake in skeletal muscle by thiazolidinediones are well documented [71]. Stimulation of lipogenesis reduces circulating non-esterified fatty acids (NEFA), thereby facilitating glucose uptake by muscle and insulin-sensitive adipocytes; hepatic gluconeogenesis is reduced. Recently, a mitochondrial target for thiazolidionediones has been described [72].

21.2.2.2 Efficacy

When used as monotherapy, thiazolidionediones can reduce fasting plasma glucose by 2–3 mmol/l and lower HbA1c by approximately 1.5% [2]. Visceral adipose depots may be reduced while subcutaneous adipose depots increase. Thiazolidinediones do not cause hypoglycemia nor are they associated with gastrointestinal side effects [67]. Rosiglitazone causes a small rise in total cholesterol levels, accounted for by a rise in both low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Elevations of triglyceride levels have been reported during rosiglitazone therapy [73]. Pioglitazone has little effect on total cholesterol, raises HDL cholesterol and reduces fasting triglycerides [74]. Clinical trials suggest that rosiglitazone and pioglitazone may be of value in the treatment of non-alcoholic fatty liver disease (NAFLD) [75].

21.2.2.3 Safety and tolerability

All thiazolidinediones have the propensity to cause fluid retention with increased plasma volume, reduced hematocrit, and a decrease in hemoglobin concentration. For this reason, thiazolidinediones should be avoided in patients with heart failure; precise exclusion criteria vary by cardiac status between Europe and the USA [76]. Fluid retention accounts for some of the weight gain that is commonly encountered with thiazolidinediones [77]. More recent safety concerns of thiazolidinediones have centered on (i) the impact of the drugs on cardiovascular outcomes [78], (ii) the adverse effects of bone metabolism [79, 80], and (iii) a possible bladder cancer risk of pioglitazone [81].

The European Medicines Agency (EMA) approved the use of pioglitazone and rosiglitazone in 2000, but demanded post-marketing cardiovascular outcome studies to provide long-term safety and efficacy data [64]. The thiazolidinediones enjoyed rapid growth while in parallel some other drugs with proven effects on microvascular outcomes – notably sulfonylureas – declined. The thiazolidinediones rapidly attained so-called blockbuster status despite a lack of the balance of risks and safety from long-term clinical studies or evidence of clear advantages over alternative classes of glucose-lowering drugs [82]. Rosiglitazone subsequently came under intense scrutiny with the publication in 2007 of a meta-analysis that reported a statistically significant 43% increase in risk of myocardial infarction and a 64% rise in cardiovascular death risk compared with placebo or other classes of glucose-lowering drugs [83]. A series of subsequent meta-analyses were unable to confirm or refute the concern that rosiglitazone increased the risk of myocardial infarction [84]. The results of the Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD) study were reassuring [85], although critics pointed to methodological issues that in their opinion may have precluded firm conclusions. In 2010 the EMA recommended the suspension of the marketing authorizations for all rosiglitazone-containing medications licensed in the EU. The US Food and Drug Administration (FDA) decided that rosiglitazone could remain available, but only within a stringent restricted-access risk evaluation and mitigation strategy (REMS) [13, 86]. The rosiglitazone saga took an additional twist in November 2013 with an announcement from the FDA that prescribing restrictions were to be relaxed [87]. The available evidence for pioglitazone at this point suggested some protection against athero-thrombotic vascular events, albeit at the cost of the aforementioned increased incidence of heart failure [80, 88–90]. In the light of the rosiglitazone experience, the FDA issued guidance requiring demonstration of cardiovascular safety for all new glucose-lowering agents intended for the treatment of type 2 diabetes [91, 92]. The new FDA stringency stipulated the need for randomized controlled trials involving adequate numbers of participants over

sufficiently long exposure and follow-up periods with adjudicated cardiovascular end points assessed against specified safety limits [92, 93].

Thiazolidinediones accelerate bone loss and increase the risk of fractures, particularly in older women [94]. Type 2 diabetes predisposes fragility fractures despite increased body weight and normal or higher bone mineral density. Factors such as risk of falling, regional osteopenia, and impaired bone quality may contribute to the increased fracture risk [95]. In 2011 reports of a small increase in the risk of bladder cancer during long-term pioglitazone therapy was also reported [96]. This finding led to changes in prescribing information; some countries, including France and Germany, prohibited or severely restricted the use of pioglitazone for this reason. While additional studies supported the association [81], more recent long-term follow-up data have been more reassuring, with no clear evidence of increased risk of bladder cancer in either sex for either pioglitazone or rosiglitazone [97]. An association between thiazolidinedione therapy and macular edema has been reported [98].

21.3 Insulin secretagogues

21.3.1 Sulfonylureas

Sulfonylureas have been in use for the treatment of type 2 diabetes since the 1950s. The first generation of sulphonylureas, that is, tolbutamide (short-acting) and chlorpropamide (long-acting), have largely been replaced by more potent sulfonylureas, including glibenclamide (known as glyburide in the USA and Canada), gliclazide (not available in the USA), glipizide, and glimepiride [2]. Sulfonylureas are preferred for patients who are not overweight since they often cause some weight gain. Starting doses should always be at the lower end of the dose range. The efficacy of sulfonylureas is similar to that of metformin. Irreversible deterioration of glycemic control during sulfonylurea therapy, which occurs in approximately 5–10% of patients per year, is held to be a consequence of the progressive β-cell failure of type 2 diabetes [99].

21.3.1.1 Mechanism of action

Sulfonylureas stimulate insulin secretion from β-cells. While extrahepatic metabolic effects have been postulated these do not appear to be of clinical relevance. The sulfonylurea receptor SUR1, a component of the transmembrane complex that includes the ATP-sensitive Kir 6.2 potassium channels (K-ATP channels), is the cellular target of action of sulfonylureas. Binding closes the K-ATP channels, leading to intracellular events that culminate in the release of insulin from preformed storage granules.

21.3.1.2 Place in glucose-lowering therapy

Sulfonylureas can be a good choice for older adults who eat consistently and are able to recognize and treat hypoglycemia appropriately [9]. The UKPDS demonstrated the ability of sulfonylureas to reduce the microvascular complications of diabetes [100]. The multinational Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study achieved improved outcomes with a gliclazide MR-based strategy without weight gain and with low rates of hypoglycemia [101]. Improved glycemic control in ADVANCE was associated with renoprotection and no increase in cardiovascular events or mortality [101].

21.3.1.3 Safety and tolerability

All sulfonylureas are metabolized by the liver with metabolite activity and routes of elimination varying between individual drugs. Drugs with rapidly reversible binding to the SUR receptor are less likely to be associated with hypoglycemia [102]. Factors such as duration of action, timing, and potency may influence the risk of sulfonylurea-associated hypoglycemia in older adults [103]. Avoidance of hypoglycemia is an important objective in managing diabetes, especially in older people, who are generally more vulnerable to this unwanted effect of sulfonylureas due to the frequent presence of co-morbidities [104]. Hypoglycemia may be more difficult to diagnose in older patients and if recurrent is associated with common age-related disorders, including progressive cognitive dysfunction and frailty [11, 105]. Chlorpropamide, use of which has tailed off in recent years, and glibenclamide have the highest hypoglycemia risk and should not be prescribed for older adults with type 2 diabetes [10]. Idiosyncratic side effects such as the chlorpropamide-alcohol flush are drug specific [52]. While agents such as glipizide [103] and gliclazide [106] are safer, all sulfonylureas have the capacity to cause major hypoglycemia since stimulated insulin release may continue even when blood glucose concentrations are below normal levels [107]. Furthermore, it has been proposed that intra-islet hyperinsulinemia

induced by sulfonylureas may reduce the glucagon counter-regulatory response to hypoglycemia [108]. Based on safety, efficacy, cost, and availability, a recent review recommended that glibenclamide/glyburide should not be used in people older than 60 years of age and that gliclazide should be added to the WHO Essential Medicines List (EML) for use in older people with type 2 diabetes (with other sulfonylureas, but not glibenclamide/glyburide, as acceptable alternatives) [109].

Concerns about potential cardiotoxicity of sulfonylureas date back to the 1970s but have not been satisfactorily resolved [110]. Given the increased cardiovascular risk with age and the high incidence of athero-thrombotic events among patients with type 2 diabetes this issue has important clinical implications. Cardiac and vascular smooth muscle cells express specific isoforms of the SUR, that is, SUR2A and SUR2B, respectively [111, 112]. Central to the debate is the degree of selectivity of different sulfonylureas for cardiovascular and endocrine SUR receptor isoforms, activation of the former having theoretically deleterious effects on vascular outcomes in the setting of tissue hypoxia [111]. In terms of compromising the protective effects of ischemic preconditioning some sulfonylureas appear to be more deleterious than others. Thus, glibenclamide (glyburide) reportedly impairs the cardiac response to ischemic preconditioning, a potentially detrimental action not shared by some other sulfonylureas [113, 114]. A 2013 meta-analysis of 62 trials reporting major cardiovascular events with during therapy with sulfonylureas compared with various comparators found an overall odds ratio (OR) for major cardiovascular events with sulfonylurea treatment versus comparators of 1.08 (95% CI 0.86–1.36). While this analysis detected no signal for excess cardiovascular risk with sulfonylureas the authors urged cautious interpretation of their results given the limitations of trial quality and potential underreporting of cardiovascular events and mortality [115]. While the current literature does not permit firm conclusions a reasonable view would be that sulfonylureas do not improve cardiovascular prognosis and that some members of the class may increase the risk of athero-thrombotic events [116].

21.3.2 Meglitinides

Compared with the sulfonylureas, the meglitinide analogues, which were introduced into clinical practice in the 1990s, are used much less often in clinical practice. Members of this class of glucose-lowering drugs are rapid-acting insulin secretagogues with a shorter half-life (approximately 60–90 min) compared with sulfonylureas [2]. Meglitinides close adenosine triphosphate (ATP)-dependent potassium channels on the β-cell membrane, depolarizing the β-cell. This results in the opening of calcium channels, increased calcium influx with augmentation of early phase glucose-stimulated insulin secretion [117]. The agents available in this class are repaglinide, nateglinide, and (in Japan) mitiglinide [118]. The onset of inhibition and subsequent reversal of ATP-dependent potassium channels by nateglinide is more rapid than that by repaglinide [119].

Repaglinide [120] and nateglinide [121] should be taken just before meals. If a meal is not taken the corresponding dose can be omitted [120]. This flexibility may help to avoid hypoglycemia in frail older patients or in those with dementia who have irregular eating habits [9]. Meglitinides, which preferentially act to reduce post-prandial hyperglycemia, have similar efficacy to metformin in terms of overall glycemic control [122]. Recognized disadvantages of meglitinides include their relatively high cost, potential to cause hypoglycemia, frequency of administration, and risk of drug–drug interactions [123]. Repaglinide may be associated with a risk of slight weight gain whereas nateglinide is regarded as being weight neutral [124].

21.3.3 α-glucosidase inhibitors

α-glucosidase inhibitors are widely used in some parts of the world, notably Asia [125]. In contrast, low rates of use of acarbose, the only member of the class available in the UK, primarily reflect the poor gastrointestinal tolerability of the drug and high discontinuation rates [126]. Two other α-glucosidase inhibitors, miglitol [127] and voglibose [128], are available in some countries. Frequent dosing adds to regimen complexity with acarbose; α-glucosidase inhibitors are relatively costly compared to some other classes of oral glucose-lowering agents [10].

21.3.3.1 Mechanism of action

α-glucosidase inhibitors retard carbohydrate digestion by competitive inhibition of the activity of α-glucosidase enzymes located in the brush border of the enterocytes that line the intestinal villi [129]. Binding of α-glucosidase inhibitors to these enzymes prevent breakdown of disaccharides and oligosaccharides into absorbable monosaccharides. Intestinal glucose absorption is

delayed, reducing post-prandial hyperglycemia. The secretion of gastric inhibitory polypeptide (GIP) may be reduced by α-glucosidase inhibitors whereas secretion of glucagon-like peptide-1 (7-36 amide) (GLP-1) is increased [2]. In contrast to drugs such as biguanides, sulfonylureas, and thiazolidinediones the glucose-lowering effects of α-glucosidase inhibitors such as acarbose are independent of endogenous insulin secretion [130].

21.3.3.2 Efficacy

In the UKPDS, acarbose titrated to a maximum dose of 300 mg daily in divided doses with meals appeared to be equally efficacious when given in addition to diet alone or in addition to monotherapy with a sulfonylurea, metformin, or insulin [131]. α-glucosidase inhibitors are seen as an alternative first-line oral glucose-lowering option [9]. They are associated with a low risk of hypoglycemia and some efficacy in lowering the postprandial hyperglycemia which is often present in older people with diabetes [10, 132]. When used as monotherapy in patients complying with dietary advice, α-glucosidase inhibitors may be expected to reduce peak postprandial glucose concentrations by approximately 1–3 mmol/l. In addition, there is often a reduction in fasting hyperglycemia of up to 1 mmol/l. The improvement in HbA1c associated with α-glucosidase inhibitors is generally less pronounced than with sulfonylureas or metformin, that is, approximately 0.5%, but sometimes exceeds 1% if a high dose of the drug is tolerated and dietary modifications are maintained.

21.3.3.3 Effect on cardiovascular risk factors

In the placebo-controlled Stop Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial conducted in subjects with a mean age of 55 years acarbose reduced the progression from impaired glucose tolerance (IGT) to type 2 diabetes by 25% [133]. STOP-NIDDM also reported a reduced frequency of cardiovascular events and lower incidence of new cases of hypertension with acarbose [134]. The potential of acarbose to reduce atherosclerotic cardiovascular disease is being tested in subjects with IGT in a new study, the Acarbose Cardiovascular Evaluation (ACE) trial [135].

21.3.3.4 Safety and tolerability

Acarbose has a good safety record and earlier concerns about hepatotoxicity appear to have been allayed [136]. In a randomized controlled trial of 192 patients with type 2 diabetes aged ≥ 65 years acarbose monotherapy effectively controlled blood glucose levels with no episodes of hypoglycemia and no clinically relevant changes in vital signs [126]. Most discontinuations of acarbose were due to gastrointestinal side effects such as flatulence and diarrhea (see below). In the latter study acarbose improved insulin sensitivity, an effects perhaps obtained by reducing glucotoxicity [126]. α-glucosidase inhibitors do not cause weight gain. The fermentation of unabsorbed carbohydrates in the large bowel is responsible for the aforementioned problems of flatulence, abdominal discomfort, and diarrhea [52]. Gastrointestinal side effects during acarbose therapy have been reported at approximately twice the frequency of placebo in controlled trials [137].

21.3.4 Dipeptidyl peptidase-4 inhibitors

The first DPP-4 inhibitor to be marketed was sitagliptin in 2006, with vildagliptin and saxagliptin following shortly afterwards (Table 21.2). While vildagliptin is available in Europe, the FDA deferred approval of the drug because of skin lesions in a primate model and issues of safety in patients with renal impairment. Linaglipitin and alogliptin were approved by the EMA and FDA in 2011 and 2013, respectively. Once-weekly DPP-4 inhibitors are in development [138].

21.3.4.1 Mechanism of action

The DPP-4 inhibitors counter the defective incretin effect that characterizes type 2 diabetes [139, 140]. The term 'incretin effect' refers to the greater stimulation of insulin secretion for a specified level of hyperglycemia when glucose is delivered orally rather than intravenously [141]. In health, the incretin effect is held to account for up to 70% of postprandial insulin secretion [142]. The principal incretin hormones – glucagon-like peptide-1 (GLP-1) [141] and glucose-dependent insulinotropic peptide (GIP) [143] – are secreted by the L cells of the distal ileum and colon, and the K cells of the duodenum and upper jejunum, respectively. Oral nutrients such as glucose and fat are potent physiological regulators of GLP-1 secretion and plasma levels of the incretin hormones rise within few minutes of eating [144]. GLP-1 and GIP are rapidly degraded, principally by a widely distributed proteolytic cell surface serine protease, DPP-4. By reducing the degradation of incretin hormones DPP-4 inhibitors elevate the circulating levels of these hormones [145]. GLP-1 and GIP act on

Table 21.2 Profiles of three commonly used DPP-4 inhibitors.

	Sitagliptin	Saxagliptin	Linagliptin
Dosage	25, 50, 100 mg once daily	2.5, 5.0 mg once daily	5 mg once daily
Half-life ($t_{½}$)	12.4 h	2.2–3.8 h	>113 h
24-h DPP-4 inhibition	≈80%	5 mg ≈ 55%	>90%
Elimination	Kidney (mostly unchanged)	Liver and kidney active metabolite	Liver, <5% renal
Dose adjustments for renal impairment	Moderate: 50 mg Severe: 25 mg	Moderate or severe: 2, 5 mg	No
Drug interaction potential	Low	Strong CVP3A4/5 inhibitors	P-gp or CVP3A4 inducer

Adapted from Spellman CW *et al.* Evolving treatment for patients with type 2 diabetes: current guidelines and emerging therapeutic decision-making. Medscape Multispeciality, 2012.

islet β-cell G-protein-coupled receptors to enhance glucose-stimulated insulin secretion [146]. GLP-1 potentiates glucose-dependent insulin release of preformed insulin within secretory granules; importantly from a clinical standpoint, this only occurs when circulating glucose concentrations are raised. Thus, as glucose levels return to normal the incretin-induced release of insulin is switched off and insulin levels rapidly decline. Insulin biosynthesis and increased insulin gene transcription are also induced by GLP-1 [146]. *Pari passu*, glucagon secretion from islet α-cells is inhibited [147]. In addition, GLP-1, but not GIP, retards gastric emptying and suppresses appetite via effects on the hypothalamus [146]. Thus, the deficient incretin effect in patients with type 2 diabetes results in a relative deficiency of glucose-dependent insulin secretion and incomplete suppression of glucagon level in response to meals [148]. These defects contribute to fasting and postprandial hyperglycemia.

DPP-4 inhibitors can raise fasting and postprandial levels of active incretin hormones concentrations in patients with type 2 diabetes [145]. In contrast to the more potent glucagon-like receptor agonists, DPP-4 inhibitors do not retard gastric emptying or reduce appetite [149]. To date, despite preclinical evidence of effects of GLP-1 on β-cell mass and function, no durable effect of DPP-4 inhibition on the natural history of declining insulin secretion in type 2 diabetes has been observed in clinical studies [150]. Clinically relevant differences in metabolism and safety profiles have emerged between the various DPP-4 inhibitors (Table 21.1) [151]. In general, no dose adjustment is necessary in elderly patients or in patients with mild to moderate hepatic impairment [152]. For patients with renal impairment, sitagliptin and saxagliptin require appropriate reductions in daily dosages, which are recommended according to estimated glomerular filtration rate [152].

Key points about the various gliptins are as follows:

- *Sitagliptin*: This is a competitive and reversible inhibitor of DPP-4 [153]. The drug has high bioavailability (approximately 90%) and a plasma half-life of approximately 8–14 h; the T_{max} of sitagliptin is approximately 1–4 h. In a single dose, 100 mg sitagliptin achieves near-complete inhibition of DPP-4 activity for approximately 12 h with around 80% inhibition 24 h post dose. Plasma protein binding is approximately 40%. A small proportion of the drug is metabolized by CYP3A4 and CYP2C6 with about 80% of sitagliptin being eliminated unchanged in the urine through renal tubular secretion. A reduced dose of sitagliptin, that is, 50 mg once daily, is recommended in moderate renal insufficiency, that is, creatinine clearance ≥30 to <50 ml/min. With more severe renal insufficiency or end-stage renal disease a dose of 25 mg once daily should be considered. Sitagliptin can be used patients with minor to moderate impairment of liver function.
- *Vildagliptin*: This is a reversible covalent inhibitor of DPP-4. The drug is rapidly absorbed and has a plasma half-life of approximately 1.5–4.5 h, T_{max} is 1 h [154]. The bioavailability of vildagliptin is around 85%.

A single dose of 50–100 mg vildagliptin provides almost complete inhibition of DPP-4 for approximately 12 h with 40% inhibition at 24 h. More than two-thirds of the drug is metabolized in the liver to inactive metabolites with approximately 15% of the drug being excreted unchanged by the kidney. Vildagliptin is not recommended in patients with moderate or severe renal impairment. A reduced dose, that is, 2.5 mg daily, is recommended if creatinine clearance is less than 50 ml/min. Reversible elevations in hepatic transaminase concentrations have been observed in association with vildagliptin. Liver function should be assessed before starting treatment, at 3-month intervals during the first year, and periodically thereafter. A marked rise in liver enzymes, >3x the upper limit of the normal range, or other evidence of hepatic impairment are contraindications to vildagliptin.

- *Saxagliptin*: This provides maximal inhibition of DPP-4 after approximately 2–3 h post dosing through the formation of a reversible covalent complex; the DPP-4 inhibition of saxagliptin extends to approximately 24 h. Relative to sitagliptin and vildagliptin, saxagliptin has greater specificity for DPP-4 than for either DPP-8 or DPP-9, which are members of the same gene family. Saxagliptin is eliminated by both renal and hepatic pathways [155]. Kidney metabolism of saxagliptin generates a hydroxylated metabolite that has approximately 50% of the activity of the parent compound. There is some evidence of active renal excretion of the parent compound, and blood levels of drug and metabolite are increased by renal impairment [156]. Circulating levels of saxagliptin and its metabolite are reduced if liver function is impaired.
- *Linagliptin*: This long-acting DPP-4 inhibitor has high selectivity for DPP-4 versus DPP-8 and DPP-9 [157]. Linagliptin is rapidly absorbed and inhibits plasma DPP-4 activity by >80% over 24 h [158]. Linagiptin binds extensively to plasma proteins, with elimination occurring primarily in the liver. Linagliptin is the only DPP-4 inhibitor excreted through non-renal pathways and does not require dose adjustment in older patients with kidney disease [159].
- *Alogliptin*: This highly selective inhibitor is rapidly absorbed with a T_{max} of 2 h and a mean half-life of approximately 12–21 h across all doses [160]. Alogliptin is primarily excreted unchanged in the urine, accounting for approximately 60–70% of the administered dose.

21.3.4.2 Place in glucose-lowering therapy

DPP-4 inhibitors can be used as monotherapy, in combination with metformin, a sulfonylurea, or a thiazolidinedione; the indications for the various DPP-4 inhibitors differ between countries. Combining a DPP-4 inhibitor with insulin can produce clinically meaningful improvements in glucose control [161]. The full efficacy of DPP-4 inhibitors requires the presence of residual β-cell function sufficient to generate glucose-stimulated insulin secretion. While the DPP-4 inhibitors are regarded as being weight neutral, some studies have reported modest weight loss [162]. Because insulin secretion is closely linked to the prevailing blood glucose concentration DPP-4 inhibitors carry a negligible risk of hypoglycemia [163]. If hypoglycemia occurs when a DPP-4 inhibitor is used in combination with a sulfonylurea or insulin, reducing the dose of the sulfonylurea or insulin and/or withdrawal of the DPP-4 inhibitor should be considered.

21.3.4.3 Efficacy

In clinical trials, administration of 100 mg/day sitagliptin as monotherapy reduced HbA1c from a baseline of 8% by approximately 0.8% after 24 weeks [164]. Similar efficacy has been demonstrated for other DPP-4 inhibitors [165]. At higher baseline HbA1c levels reductions in HbA1c >1% have been reported. In phase 3 trials, the tolerability of DPP-4 inhibitors has generally been good, with a low frequency of adverse events. Theoretical concerns about interference with innate immunity have been raised because DPP-4 also functions as the lymphocyte CD36 protein. However, human studies have not shown any significant untoward effects on systemic immune function [166]. Compared with placebo and comparator drugs, a slightly higher incidence of upper respiratory tract infections has been reported in phase 3 trials. However, studies of DPP-4 inhibitors in populations including elderly patients and those with renal impairment have not confirmed an increased risk of infection [167].

21.3.4.4 Safety and tolerability

DPP-4 inhibitors have tolerability profiles that approximate to those associated with placebo in clinical trials [168]. Safety concerns relating to DPP-4 inhibitors have focused on pancreatitis [169], pre-neoplastic lesions [170], and heart failure [171]. Post-marketing events of acute pancreatitis, including fatal hemorrhagic or necrotizing pancreatitis, were reported in patients

receiving sitagliptin, vildagliptin, and saxagliptin. Concerns were also raised about pancreatic duct metaplasia during DPP-4 inhibitor therapy [172]. In 2014, the FDA and EMA evaluated the pancreatic safety of DPP-4 inhibitors, stating that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer were inconsistent with the available data [173]. However, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal.

As discussed above, since 2008 the FDA has required cardiovascular outcome trials of new diabetes therapies [174]. When saxagliptin was approved by the FDA in 2009 one of the post-marketing requirements was to demonstrate lack of cardiovascular toxicity [175]. The phase 4, multicentre Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-THrombolysis in Myocardial Infarction (SAVOR-TIMI 53) study is the first example of a post-approval commitment under the new FDA guidance. An increase in risk of hospital admissions for heart failure was observed with saxagliptin in SAVOR-TIMI 53; this was an unexpected finding that had not been predicted by preclinical or clinical studies [176]. In the case of alogliptin, the EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) trial was commenced prior to registration to evaluate the cardiovascular safety of alogliptin versus placebo in addition to standard care in subjects with type 2 diabetes and acute coronary syndromes [4]. No heart failure signal was observed in the smaller EXAMINE trial [177]. However, there was evidence of heterogeneity in EXAMINE with respect to the primary endpoint in several subgroups, including patients who had a known diagnosis of diabetes longer than 10 years' duration [177]. The results of SAVOR have generated concerns about whether heart failure might be a class effect of DPP-4 inhibitors [178, 179]. The results of the ongoing (as of May 2015) Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study are expected to help resolve this issue [180]. Interim data from TECOS have been reassuring. In April 2015, the Endocrinologic and Metabolic Drugs Advisory Committee voted to update the labels for saxaglipitin and alogiptin primarily on the 27% increase in the rate of the first event of hospitalization for heart failure.

21.3.5 Sodium-glucose co-transporter type 2 inhibitors

Approximately 160–180 g of glucose is filtered daily via the kidney into the urine in healthy adults [181]. Reabsorption of glucose is proportional to the filtered glucose load until the transport maximum is exceeded. Glucose requires carrier proteins to move across cell membranes. Sodium-glucose co-transporter-1 (SGLT1) and SGLT2 reabsorb 10% and 90%, respectively, of filtered urinary glucose [181]. Glucose reabsorbed via SGLT1 and SGLT2 is then reabsorbed into the circulation via the GLUT1 and GLUT2 glucose transporters, respectively [182]. SGLT2 is expressed almost entirely on proximal renal tubule cell membranes. This low-affinity high-capacity transporter couples reabsorption of each glucose molecule to a sodium ion [183]. SGLT1 is also expressed in the enterocytes of the small intestine [184].

A new class of glucose-lowering agents, the SGLT2 inhibitors, have recently become available and their pharmacological actions defined [185]. These drugs – dapagliflozin [186] (approved in the EU in 2012 and the USA in 2014), canagliflozin [187] (approved by the FDA and EMA in 2013), empagliflozin [188] (approved by the FDA and EMA in 2014), and ipragliflozin [189] (approved in Japan in 2014) – offer a complementary approach to glucose-lowering with some advantages over more traditional agents.

21.3.5.1 Mechanism of action

SGLT2 inhibitors promote renal glucose excretion, thereby reducing blood glucose concentrations [190] (Figure 21.1). The amount of glucose excreted in the urine during SGLT2 inhibitor therapy depends on both the level of hyperglycemia and the glomerular filtration rate. Since the mechanism of SGLT2 inhibition is independent of circulating insulin levels or insulin sensitivity these agents can be combined with all other classes of glucose-lowering drugs, including exogenous insulin [191].

Mechanistic studies of SGLT2 inhibitors have yielded evidence of wider indirect effects on metabolic regulation [192]. In a study in men with type 2 diabetes treated for 14 days with dapagliflozin whole-body glucose disposal increased during dapagliflozin therapy and remained unchanged in placebo-treated subjects [193]. The improvement in insulin sensitivity was interpreted as congruent with the glucose toxicity

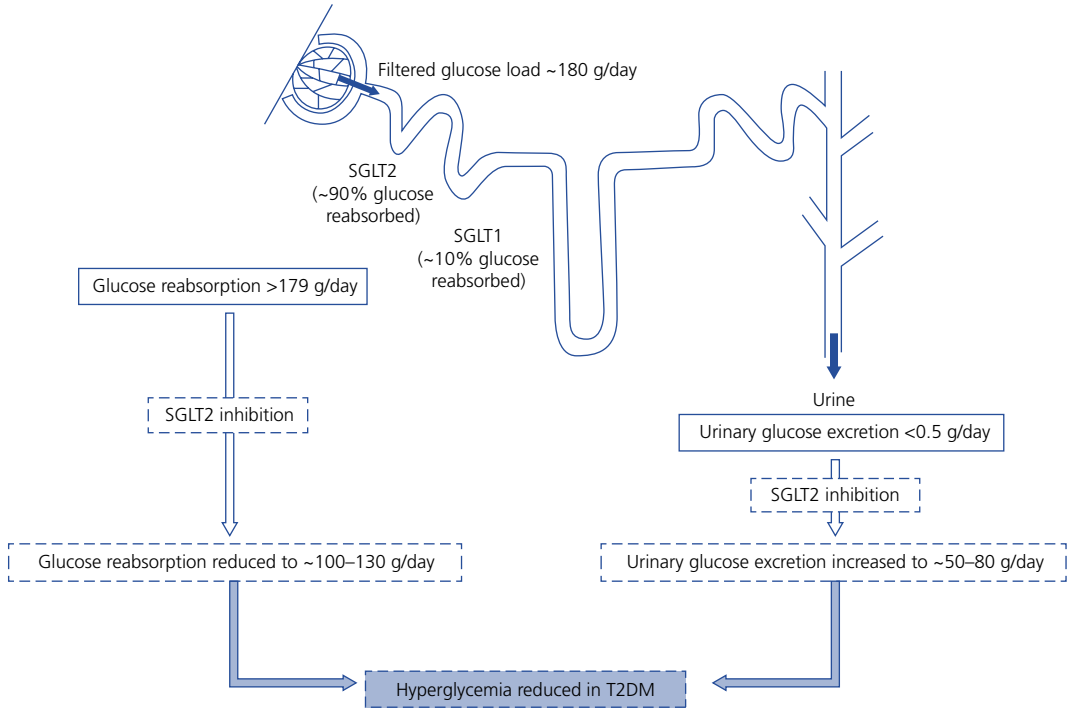

Figure 21.1 Renal tubular reabsorption of glucose. T2DM, type 2 diabetes mellitus; SGLT2, sodium-glucose co-transporter-2. Adapted from Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Dovepress Open Access 2014; 2014: 1335–80.

hypothesis, that is, that lowering blood glucose (in this scenario by promoting renal glucose excretion) leads to improved insulin action [194]. However, dapagliflozin was associated with a paradoxical increase in endogenous glucose production ($p < 0.05$ vs placebo) [193]. The increase in endogenous glucose production was almost identical to the amount of glucose excreted in the urine in the dapagliflozin-treated subjects. An increase in the fasting level of the insulin-antagonistic hormone glucagon was also observed. Subsequent studies demonstrated SGLT2 expression in the glucagon-secreting α-cells of the pancreatic islets and stimulation of glucagon secretion by dapagliflozin in an animal model [195]. In a study of empagliflozin in patients with type 2 diabetes a similar increase in endogenous glucose production was observed, which detracted from the therapeutic effects of the SGLT-2 inhibitor on plasma glucose. As would be expected, plasma insulin declined in response to the lowering of blood glucose, whereas plasma glucagon levels increased [196].

21.3.5.2 Efficacy

Head-to-head trials of up to 2 years' duration have demonstrated that SGLT2 inhibitors have similar glucose-lowering activity to metformin, sulfonylureas, or sitagliptin [6, 12]. The place of SGLT2 inhibitors in treatment algorithms is still being evaluated [197]. Based on their putative mode of action SGLT2 inhibitors were predicted to carry a low risk of hypoglycemia; this has proved to be the case in clinical trials to date [6]. The absence of hypoglycemia represents an obvious advantage in older patients. Urinary calorie loss, which can reach 200–300 kcal/day during treatment with SGLT2 inhibitors, promotes reductions in body weight [198, 199]. Consistent reductions in blood pressure have been described [5]. Some heterogeneity in changes seen in lipid profiles between individual drugs has been described [5].

21.3.5.3 Cautions and contraindications

The pharmacodynamic response to SGLT2 inhibitors declines with increasing severity of renal impairment [6]. Accordingly, the prescribing information for each

SGLT2 inhibitor should be consulted with respect to dosage adjustments or restrictions in moderate to severe renal dysfunction; recommendations differ between agents in this class. Caution is also recommended in the elderly population because of a higher risk of dehydration, orthostatic hypotension, and acute impairment of renal function (see below) [200]. The effect of SGLT2 inhibitors on the risk of cardiovascular disease is presently being evaluated in several ongoing prospective placebo-controlled trials [201].

- *Dapagliflozin*: This is a selective SGLT2 inhibitor that is rapidly and absorbed after oral administration with maximal plasma concentrations occurring within 2 h of administration [202]. Bioavailability is approximately 80% at 10 mg once-daily dosing. Dapagliflozin metabolism occurs predominantly in the liver and kidneys to the major metabolite dapagliflozin 3-O-glucuronide, which does not demonstrate SGLT2 inhibitor at clinically relevant exposures. Dapagliflozin is not appreciably cleared by renal excretion with <2 % of a dose recovered in urine as the parent drug [202]. Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment, that is, creatinine clearance <60 ml/min or eGFR <60 ml/min/1.73 m^2. Dapaglifozin can be taken with or without food and is highly protein-bound. Dapagliflozin is commenced in a dose of 5 mg daily, which can be increased to 10 mg if required. Mechanistically, it has been demonstrated that dapagliflozin increases urinary glucose excretion in patients with type 2 diabetes by reducing the maximum renal glucose reabsorptive capacity and threshold at which glucose is excreted in the urine [203]. Treatment with dapagliflozin reduces HbA1c by an average of 0.50%, fasting plasma glucose by 1 mmol/l, weight by 2 kg, body mass index by 1.1%, and systolic and diastolic blood pressure by 4 and 2 mmHg, respectively, over 24–52 weeks [204]. Dapagliflozin improves glycemic control in patients with type 2 diabetes in clinical trials as monotherapy and in combination with metformin, glimepiride, pioglitazone, sitagliptin, or insulin [205]. An imbalance in the incidence of female breast cancer and male bladder cancer was noted in phase 3 clinical trials of dapagliflozin [206]. This finding caused the FDA to initially reject dapagliflozin in 2012. Preclinical animal toxicology had not suggested a cancer risk of dapagliflozin, nor was an excess of cancer observed in clinical trials of canagliflozin [206]. Tumorigenicity studies, including studies of human bladder transitional cell carcinoma cell lines, have shown no adverse effects of dapagloflozin [207]. The FDA has demanded post-marketing studies to determine whether dapagliflozin is associated with increased risks of cardiovascular events, liver toxicity, or malignancies. In the light of the numerical excess of bladder cancers, dapagliflozin is not recommended for patients with active bladder cancer.
- *Canagliflozin*: This is a selective inhibitor for SGLT2 that lowers the renal threshold for glucose to approximately 4.5 mmol/l, thereby increasing the urinary excretion of glucose [208]. At 300 mg per day or higher, canagliflozin may also inhibit intestinal SGLT1 [209]. While SGLT1 only plays a minimal role in glucose reabsorption, inhibiting both SGLT1 and SGLT2 may lower postprandial hyperglycemia [209]. Canagliflozin reaches peak plasma concentrations within 1–2 h following oral administration, with steady state levels being reached in 4–5 days. The drug has a bioavailability of 65% and is highly protein bound. With continued dosing the renal threshold is reduced throughout the 24-h period, allowing once-daily dosing. Metabolism is mainly to inactive metabolites, which are renally eliminated. Cytochrome P450 metabolism is minimal, thereby reducing the potential for drug–drug interactions. Approximately 33% of canagliflozin metabolites are eliminated via the renal route and approximately 40% is excreted in the feces. As monotherapy in adults with type 2 diabetes aged 18–80 years, canagliflozin 100 mg and 300 mg reduced baseline HbA1c by 0.77% and 1.03%, respectively, which led to a least squares mean difference of −0.91% and −1.16% compared with placebo (−0.14%) [210]. Canagliflozin reduces body weight and systolic blood pressure, and carries a low risk of hypoglycemia [211]. However, increases in plasma levels of LDL cholesterol have been observed compared with placebo [212]. Weight reduction associated with canagliflozin is predominantly attributable to decreased adiposity rather than water loss [213]. Reductions in HbA1c and systolic blood pressure appear to be mediated via weight-loss-associated and weight-loss independent mechanisms, the latter having the larger effect [214]. Genital mycotic infections were observed in a higher percentage of both males (4.1%) and females (8.1%) receiving

canagliflozin compared with those receiving placebo (no cases in males, but 3.9% of females). Most of the infections were judged to be of mild to moderate severity and were effectively treated with oral or topical treatments; a small increase in the risk for urinary tract infections was also noted in clinical trials of canagliflozin [211]. The therapeutic actions of canagliflozin have been observed in older patients with type 2 diabetes [215]. A review of the literature concluded that canagliflozin appeared to be well tolerated in older subjects, with a safety profile that was consistent with that of other phase 3 trials in the general population [215]. However, in older patients, especially when there is an underlying chronic kidney disease or congestive heart failure, greater caution is required with SGLT2 inhibitors [216]. In the case of canagliflozin the dose requires adjustment based on renal function. A maximum dose of 100 mg daily should be used in those with an eGFR between 45 and 60 ml/min. If the eGFR falls below 45 ml/min, canagliflozin should not be used.

The FDA has expressed concerns about potential adverse cardiovascular effects of canagliflozin, which was initially rejected in 2012 [217]. In a study of patients at high risk of cardiovascular disease 13 participants in the canagliflozin treatment arm sustained a major cardiovascular event compared with only one placebo-treated subject within the first 30 days of treatment, but this imbalance was subsequently reversed over time. Small increases in HDL cholesterol and LDL cholesterol have been observed with canagliflozin compared with placebo [218]. The FDA considered that the available data were insufficient to be certain about the magnitude of any excess risk of vascular events and concluded that longer-term follow-up would be required, including completion of the CANagliflozin cardioVascular Assessment Study (CANVAS) [219].

Another reported side effect of canagliflozin treatment is osmotic diuresis, loss of body water, and hemoconcentration. This is regarded as a class effect of SGLT2 inhibitors in general. In contrast to classical osmotic diuresis SGLT2 inhibition also causes sodium loss [220]. This natiuresis is explained by the co-transportation of sodium with glucose by SGLT2. The absence of hypernatremia poses a risk to elderly patients who may not develop sufficient thirst to compensate for water loss. This may lead to dehydration, hypotension, and syncope [6, 11, 215]. In order to avoid hemodynamic problems in vulnerable patients, canagliflozin therapy should be initiated with the lower dose of 100 mg per day instead of 300 mg per day. Concomitant use of canagliflozin and loop diuretics is not recommended. The impact of SGLT2 inhibitors on renal function and course of diabetic nephropathy merits more attention by clinicians and researchers.

- *Empagliflozin*: This is a selective inhibitor of SGLT2 that provides dose-dependent increases in urinary glucose excretion [221]. Based on pharmacokinetic studies no dose adjustment is required in the presence of renal or hepatic impairment [222, 223]. As monotherapy, empaglifozin is an option for patients in whom diet and exercise alone do not provide adequate glycemic control and when metformin is considered inappropriate. The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and in whom tighter glycemic control is required, the dose can be increased to a maximum of 25 mg once daily.

21.4 Other oral glucose-lowering drug options

21.4.1 Colesevelam

Colesevelam is a second-generation bile acid sequestrant with effects on both blood glucose and lipids [224]. Colesevelam was approved by the FDA for use in type 2 diabetes in 2008. Colesevelam may be used as monotherapy and in combination with other classes of glucose-lowering drugs. In clinical studies colesevelam, added to existing metformin, sulfonylurea or insulin therapy, reduced HbA1c levels by a mean of 0.5% [225]. Postulated mechanisms of glucose lowering include effects on the farnesoid X receptor (the bile acid receptor) and TGR5 (a G protein-coupled receptor) within the intestine as well as effects on farnesoid X receptor within the liver [226, 227]. Activation of TGR5 has been proposed to affect secretion of incretin hormones, particularly GLP-1 [228]. Because colesevelam is not systemically absorbed its use is not contraindicated in patients with renal or hepatic impairment or heart failure. Colesevelam is generally well tolerated [229]. The main side effect of colesevelam is constipation. The drug should not be used in patients with

gastroparesis or other gastrointestinal motility disorders, in patients after major gastrointestinal surgical procedures, and in others at risk for bowel obstruction [230]. Other reported side effects include an increase in the level of serum triglycerides and possible malabsorption of fat-soluble vitamins. Colesevelam has a low risk of hypoglycemia and is not associated with weight gain [231]. In the context of treating primary hyperlipidemia and type 2 diabetes in older patients, colesevelam is reportedly as safe, well tolerated, and efficacious in patients aged ≥65 years as in those aged <65 years [232, 233].

21.4.2 Bromocriptine

Bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) was approved by the FDA for the treatment of type 2 diabetes in 2009. In the fasting state, peak concentrations of the drug are attained within 60 min of oral dosing. Absorption is delayed by food, and peak plasma levels are achieved at ~120 min in the fed state. The drug appears to enhance reduced morning central nervous system dopaminergic activity in patients with type 2 diabetes, resulting in improved insulin sensitivity and reduced hepatic glucose output [234]. Phase II and III studies have shown that bromocriptine-QR lowers HbA1c by 0.6–1.2% as monotherapy or in combination with other glucose-lowering medications [235]. Treatment with bromocriptine-QR appears to be associated with a minimal risk of hypoglycemia, with no clinically significant adverse effects on body weight, triglycerides, or blood pressure [236]. The most common adverse effect of bromocriptine-QR is nausea. A reported reduction in cardiovascular events in a placebo-controlled prospective safety study of bromocriptine-QR in patients with type 2 diabetes awaits confirmation [237, 238].

21.5 Oral glucose-lowering drugs in development

Several classes of new orally active glucose-lowering drugs are reported to be in clinical development (Table 21.3).

21.5.1 Peroxisome-proliferator activated receptor agonists

The efficacy and safety of pairing the metabolic benefits of thiazolidinediones with the lipid-modifying effects of fibric acid derivatives has led to the creation of combined PPAR-α/PPAR-γ agonists, also known as glitazars. Improvements in glucose and lipid metabolism have raised hopes of beneficial effects on cardiovascular disease [239]. However, the development of several agents has been discontinued because of a range of toxicity problems. Muraglitazar, which improved aspects of insulin action and lowered glucose and triglyceride levels [240], was found to be associated with an excess incidence of the composite end point of death, major adverse cardiovascular events, and congestive heart failure compared to placebo and pioglitazone [241]. Efforts continue to develop novel insulin-sensitizers that preserve the glucose and positive lipid-modifying effects of the thiazolidinediones while avoiding the adverse issues of fluid retention, heart failure, and osteopenia [242].

Table 21.3 Examples of novel glucose-lowering drugs in development for the treatment of type 2 diabetes.

PPAR-modulators
Selective peroxisome proliferator-activated receptor-γ modulators (SPPARMs)
Sulfonylurea receptor modulators
Glucokinase activators
GPR119 agonists
Glucocorticoid pathway modulators
Peroxisome-proliferator activated receptor
GPR119: G protein-coupled receptor 119

21.5.2 Glucokinase activators

Glucokinase is a member of hexokinase family of enzymes that are responsible for the phosphorylation of glucose to glucose-6-phosphate. The enzyme has a key role in maintaining glucose homeostasis in islet β-cells and hepatocytes [243]. Drugs that activate glucokinase have entered clinical trials [244, 245]. However, to date glucokinase activators have generally not progressed beyond phase 2 of clinical development. Lack of durability of glucose-lowering effect has been observed with some glucokinase activators [246–248]. Theoretical concerns include the risk of delayed recovery from hypoglycemia, although data from clinical mechanistic studies have been reassuring on this point [249, 250]. Another concern with glucokinase activators is the potential for development of fatty liver disease and dyslipidemia [248, 251].

21.6 Conclusions

All drugs used for lowering blood glucose in patients with type 2 diabetes have limitations in terms of long-term efficacy and the potential for adverse – potentially fatal in some circumstances – effects. The arrival of drugs with novel modes of action that can be used alongside more established agents is welcome. However, caution is required until the risk–benefit profiles of newer agents are fully evaluated. The lessons of the rosiglitazone controversy have strengthened regulatory requirements for new glucose-lowering drugs. However, the potential for the emergence of unpredictable serious adverse effects after many years of clinical use underlines the need for circumspection and pharmacovigilance.

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CHAPTER 22
Insulin therapy

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KEY MESSAGES

- Insulin therapy is underutilized in older people with diabetes due to concerns about the complexity of administration and risk of hypoglycemia.
- The future need for insulin therapy should be addressed early in the course of the disease.
- Insulin analogs are safer choices than their human counterparts.
- Pen devices significantly reduce dosing errors and risk of hypoglycemia.
- Glycemic target and insulin regimen should be individualized.

22.1 Introduction

The estimated prevalence of diabetes mellitus among those aged 65 years and older in the USA ranges from 22% to 33%. This prevalence is expected to grow further as the US population ages, making diabetes a significant healthcare burden for the elderly population [1]. For example, diabetes in older people is responsible for 30–40% of all hospitalizations and 30–60% of all nursing home admissions [2]. The treatment of diabetes mellitus is becoming increasingly complex as physicians are required to choose between a growing number of oral and injectable therapies, including insulin. Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion at diagnosis and by progressive β-cell dysfunction over time. The progressive loss of β-cell mass and function often leads to decreased effectiveness and eventual failure of non-insulin hypoglycemic medications alone. Insulin therapy is thus frequently required during the course of the disease to maintain glycemic control and to prevent diabetes complications. However, as patients with diabetes get older, they face a unique set of challenges, including the emergence of geriatric giants such a cognitive dysfunction, depression, visual and/or hearing impairment, and physical disabilities, leading to difficulties in performing activities of daily living. This is in addition to the coexisting medical co-morbidities that make it difficult for them to maintain the self-care necessary for their diabetes management. The additional burden of polypharmacy may also increase the risk of adverse effects due to drug interactions. Furthermore, elderly patients often live alone, which may make them more vulnerable to significant consequences of hypoglycemia. Therefore, starting insulin therapy and which regimen to use in this age group should take into account several factors, including the patient's acceptance and willingness to adhere to this therapy. This chapter reviews insulin therapy in older people with diabetes and highlights special clinical issues unique to this age group.

22.2 Indications for insulin therapy

The general principle of insulin use is the achieving of as normal a glycemic profile as possible without significant side effects, regardless of age. Long-term

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treatment goals are to prevent or slow down the development of microvascular and macrovascular complications of diabetes mellitus through good glycemic control and avoiding prolonged hyperglycemia. In the elderly, persistent hyperglycemia should be avoided to prevent the development of a hypercatabolic state, which leads to muscle wasting or sarcopenia and frailty. Minimizing hyperglycemia is also important for maintaining cognitive function, therefore insulin therapy is indicated when symptomatic hyperglycemia with weight loss, nocturia, polydipsia, and fatigue occurs or signs of severe insulin deficiency, such as ketosis, are present despite the use of multiple non-insulin hypoglycemic agents. Insulin initiation is indicated when fasting plasma glucose levels are frequently >14 mmol/l, random glucose levels are consistently >17 mmol/l, or HbA1c is above 10% [3]. Other indications include concomitant medical conditions or acute medical illness. Earlier insulin therapy may be indicated in the presence of renal, cardiovascular or hepatic impairment that could interfere with the use of non-insulin hypoglycemic agents. In patients newly diagnosed with diabetes, insulin can be initiated as a first-line therapy if diabetes is grossly uncontrolled with symptomatic hyperglycemia and metabolic decompensation. Non-specific ill-health or malaise associated with chronic hyperglycemia is another indication for insulin therapy (Box 22.1).

22.3 Advantages and disadvantages of insulin therapy

Insulin is the most effective hypoglycemic agent, regardless of age. Patients aged >70 years can achieve the same level of glycemic control from insulin as

Box 22.1 Indications for insulin therapy.

Persistent symptomatic hyperglycemia despite non-insulin therapy [3]

- Fasting glucose level consistently >14mmol/l
- Random glucose level consistently >17mmol/l
- HbA1c level >10%

Presence of hyperglycemic complications

- Increased confusion
- Dehydration
- Infections

Signs of insulin deficiency

- Ketosis
- Ketonuria
- Weight loss

Concomitant diseases that preclude use of non-insulin agents

- Pancreatitis
- Hepatic cirrhosis
- Renal failure
- Cardiac failure
- Chronic steroid therapy
- Chronic inflammatory disease
- Antirejection therapy

Acute medical illness with acute decompensation

younger patients [4]. Insulin treats hyperglycemia in all patients, leading to a better quality of life and wellbeing. It also has a powerful anabolic effect, limiting muscle wasting and sarcopenia. Elderly patients with poor glycemic control and weight loss will benefit from insulin therapy since it is usually associated with weight gain. The main side effects associated with insulin therapy are the inconvenience of frequent injections and blood glucose monitoring, weight gain in obese patients (although it may be beneficial in certain frail patients), and the risk of hypoglycemia, which may be significant in older people. Several factors may contribute to the greater frequency of hypoglycemia in older than in younger people. For example, older people with diabetes may have impaired hepatic or renal function, leading to poor hypoglycemic medications metabolism and/or clearance. They are also more likely to receive multiple medications, which makes them more susceptible to hypoglycemia resulting from drug interactions. It has been shown that two-thirds of hospitalizations after emergency room visits in the USA by older people >65 years of age were due to unintentional drug overdose. Nearly half of these hospitalizations were among those ≥80 years old (48.1%; 95% CI 44.6–51.6). Insulin was responsible for 13.9% of cases and rated second (to warfarin), and oral hypoglycemic agents were responsible for 10.7% of cases and rated fourth of the drugs with the most adverse drug events in the elderly resulting in emergency hospitalizations [5] (Box 22.2).

Box 22.2 Advantages and disadvantages of insulin therapy.

Advantages

- Most effective hypoglycemic agent
- Treats hyperglycemia regardless of age
- Can be tailored rapidly to changes in need during acute Illness
- Improves quality of life and wellbeing
- Treats acute hyperglycemic complications such as:
  - infections
  - dehydration
  - confusion
  - ketoacidosis
- Insulin has potential powerful anabolic effects:
  - helps wound healing
  - prevents muscle wasting
  - delays development of frailty
  - weight gain in frail patients

Disadvantages

- Inconvenient:
  - frequent injections
  - frequent blood glucose monitoring
- Weight gain in obese patients
- Risk of hypoglycemia

22.4 Barriers to insulin therapy

The most common barrier to insulin therapy is the fear of needle pain and the inconvenience of multiple injections, complexity of administration and frequent blood glucose monitoring [6]. Major limitations also include inability to self-administer due to poor vision, impaired manual dexterity, poor functioning or impaired cognition. Another patient concern is the fear of hypoglycemia and weight gain. Patients may perceive their need for insulin as a failure to control their disease. Patients failing to start insulin commonly report misconceptions regarding insulin therapy. In one study, 35% of patients believed that insulin causes blindness, renal failure, amputations, heart attacks, strokes or early death [7]. There is also resistance on the part of healthcare providers, who may delay insulin therapy and continue using multiple oral medications past their clinical effectiveness in an effort to avoid exposing patients to the possible side effects of insulin. In the very elderly, the perceived negative impact of insulin therapy on the patient's independence and daily routine by healthcare professionals may be considered to outweigh the potential health benefits [8]. Cultural specific barriers to insulin therapy also exist. Studies on psychological insulin resistance amongst multi-ethnic populations have found that ethnicity is an important determining factor. Ethnic minorities living in western countries are less willing to start insulin therapy [9]. Reasons for this resistance include language barriers between patients and healthcare provider, and health system-related barriers such as perceived lack of access to care and lack of resources [10] (Box 22.3).

Box 22.3 Barriers to insulin therapy.

Patient related

- Fear of needles and pain
- Fear of hypoglycemia and weight gain
- Complexity and inconvenient frequent blood glucose monitoring
- Inability to self-administer due to:
  - poor vision
  - impaired manual dexterity
  - poor physical function
  - impaired cognition
- Misconceptions about insulin:
  - own failure and self-blame
  - insulin is a stigma
  - religious beliefs

Physician related

- Negative impact on patient lifestyle
- Negative attitude towards insulin
- Fear of hypoglycemia
- Lack of experience or training

Healthcare system related

- Lack of resources
- Commu nications and continuity of care
- Language barriers
- The availability of carers and diabetes support team

22.5 Goals of insulin therapy

There are three main factors to consider before setting glycemic targets in older people: limited life expectancy, complexity of chronic conditions, and the limits of care time given the number of healthcare issues that must be addressed [11]. Older people with diabetes mellitus are heterogeneous and vary widely in duration of diabetes, functional status, presence of comorbidities, and complications, therefore the goals of therapy should be individualized. Managing insulin therapy in the elderly can also be challenging because of the frequent presence of cognitive deficits, physical disability, and geriatric syndromes, which may increase the risk of hypoglycemia due to possible drug interactions and incorrect doses. There are also no direct data from clinical trials conducted in older people regarding optimum targets in this population. An HbA1c of 7.0% is generally recommended for non-frail elderly patients, which can be achieved with a fasting or pre-meal glucose maintained around <7.0 mmol/l and postprandial glucose around <10 mmol/l [12]. On the other hand, a less stringent HbA1c goal (around 7.5–8.0% or higher) is appropriate for patients with a history of severe hypoglycemia, advanced complications, multiple comorbidities or limited life expectancy [13]. It is important to realize that hypoglycemia can still occur in older people with relaxed HbA1c, suggesting that relaxed targets are not protective enough to prevent hypoglycemia and reinforcing the idea that targets in the elderly should be individualized [14]. A clinical decision based on the patient's functional status and their wishes is therefore appropriate. The ultimate goal is to provide the patient with an individually tailored, flexible regimen that maintains health and quality of life. The aim of insulin therapy is to reduce potential diabetes complications without imposing undue self-management burdens or exposing the patient to the risk of adverse side effects such as hypoglycemia and/or weight gain.

22.6 Initiation of insulin therapy

Insulin therapy is usually delayed due to reluctance by healthcare professionals and patient fear of side effects. In an epidemiological study, the population HbA1c values were as high as 10% prior to initiation of insulin therapy [15]. Delaying insulin treatment with persistent hyperglycemic burden may lead to frustration, low motivation, less active self-care, and eventually exacerbate co-morbid depression [16]. Early use of insulin in the treatment strategy is recommended. Thus, when patients are taking high doses of oral hypoglycemic medications, any deterioration of glycemic control should trigger consideration of insulin therapy [3]. Introducing older people with uncontrolled diabetes early on to existing oral hypoglycemic medications has been shown to be more effective than increasing oral doses alone (HbA1c reduction of 1.5% with insulin vs 0.6% with increased oral doses). Also hypoglycemic events were lower with insulin than with increased oral medication doses (23 vs 79, $p = 0.03$), indicating that adding insulin early on may be a safer option than increasing the doses of oral

hypoglycemic medications [17]. Continuation of oral hypoglycemic medications should be considered when initiating insulin therapy. This can result in greater HbA1c reduction and lower daily insulin requirements with lower hypoglycemic risk and less weight gain. When initiating insulin therapy, patients need to know that this represents a natural course of the disease and is not a failing on their part. Insulin initiation is often linked to patients' feelings of blame and failure [18], therefore healthcare professionals should address this misconception by counseling patients at an early stage of the illness. Educating patients about the progressive nature of the disease, the need for insulin as a natural step of therapy, and that the addition of insulin will help to alleviate symptoms of hyperglycemia and prevent complications may help gain patient acceptance of insulin therapy. Patient education promotes compliance. Although patients may accept insulin therapy, this does not necessarily mean that they will be able to implement effective self-care. An important element of self-care is the ability of the patient to comply with treatment recommendations. Because of the high prevalence of cognitive impairment and other geriatric syndromes in older people, clinicians should perform a comprehensive assessment of patients' ability to administer and monitor insulin therapy and recognize and treat hypoglycemia. The time for the initiation of insulin is right when an informed and motivated patient feels his or her own treatment goals are no longer being met with non-insulin therapy and at this point a dialog between patient and healthcare professional can lead to ready acceptance of the need to initiate insulin. Most patients feel better when their glucose levels are under good control, which is a major motivation for initiating and adhering to insulin (Box 22.4).

22.7 Physiologic insulin secretion

The pancreas produces a physiologic bolus of insulin secreted at mealtimes (prandial) in proportion with the carbohydrate intake in addition to a constant (basal) production of insulin.

22.7.1 Prandial insulin secretion

The plasma glucose concentration of healthy individuals remains constant within a normal range despite large fluctuations in carbohydrate intake and physical activity. This is regulated by a balance between insulin secretion from the β-cells of the pancreas and insulin action on sensitive tissues such adipose tissue, liver, and muscle. After meal consumption by a healthy individual, plasma glucose concentration increases rapidly in the first 30–60 min and returns to basal level within 2–3 h [19]. Physiologic insulin secretion follows the same pattern. Initially, the insulin response to glucose intake is characterized by a rapid increase in insulin secretion that is completed within 10 min (first phase). This is followed by a sustained secretion of insulin above basal rates, which lasts for several hours before declining to basal rates (second phase) [20]. Patients with diabetes will need replacement of insulin that mimics these physiologic phases of insulin secretion. Insulin administered at mealtimes to mimic the first phase response of insulin production is called prandial insulin. It should have a fast onset of action to cover the initial elevation in glucose. A lag time is needed between insulin subcutaneous injection and food consumption to allow time for insulin absorption from the subcutaneous site and the initial glucose rise. The more fast acting the insulin, the shorter the lag time needed before food consumption.

22.7.2 Basal insulin secretion

Once food has been absorbed and glucose is no longer elevated in the bloodstream (the normal fasting or post-absorptive state) hepatic glucose production increases while the secretion of insulin is inhibited. This "basal insulin" concentration is the amount of insulin required in the post-absorptive state to restrain endogenous glucose output primarily from the liver, and modulate muscle and other tissue uptake. Patients with diabetes mellitus will therefore need a constant level of insulin between meals and overnight (basal insulin) to cover hepatic glucose release.

22.8 Insulin regimens

Three types of insulin regimen are commonly used: basal, premixed, and basal-bolus. Each regimen presents benefits and risks, balancing improved glycemic control with potential risk of hypoglycemia and/or weight gain. None of these regimens typically reflects normal physiologic insulin secretion. Studies in which different regimens have been compared are scarce. Wolffenbutel *et al.* [21] compared three different insulin

Box 22.4 Practical issues before initiating insulin therapy.

Patient counselling

- Natural course of the disease
- The need and benefits of insulin
- Patient acceptance to insulin therapy
- Glycemic goals
- Hypoglycemia risk

Patient assessment

- Cognition and mood
- Ability to administer insulin
- Ability to recognize and treat hypoglycemia
- Ability to monitor blood glucose
- Availability of carers and support at home

therapy regimens (alone or in combination with oral hypoglycemic medications) in elderly patients (average age 68 years) and found no preferences for any specific regimen. Because there is not enough evidence available to suggest the optimal regimen in older patients with diabetes, the choice of insulin regimen is normally based on healthcare professional experience as well as patient preference and specific patient considerations, including general health, glycemic goals, and lifestyle factors. Reduced frequency of injections and simplicity of titration are desirable features for patient compliance.

22.8.1 Basal insulin regimen

The most convenient and simple way to initiate insulin therapy in older people with diabetes is to use long-acting basal insulin at bedtime because of its effectiveness, simplicity, and once-daily dosing. Basal insulin provides relatively uniform insulin coverage throughout the day and night, mainly to control blood glucose by suppressing hepatic glucose production in between meals and during sleep. Basal insulin alone is usually added to existing oral hypoglycemic medications, starting at 0.1–0.2 U/kg body weight following a "start low and go slow" policy. Patients can be taught to up-titrate their own insulin by a small dose increments if hyperglycemia persists, guided by fasting blood glucose level. The addition of 1–2 units to the daily dose once or twice weekly if the fasting glucose levels are above the pre-agreed target is a reasonable approach. When the target is getting closer, dosage adjustments can be less frequent and reduced. Downward adjustment is advisable if any hypoglycemia occurs. Initially daily blood glucose monitoring is important until stabilization of insulin dose. Basal insulin analogs such as glargine and detemir provide an extended duration of constant peakless insulin absorption that more closely resembles normal basal insulin secretion than does intermediate-acting human insulin such as neutral protamine hagedorn (NPH) [22]. Long-acting insulin analogs are associated with less glucose variability than NPH, therefore they are the preferred agents in elderly patients due to ease of administration and decreased risk of hypoglycemia, especially nocturnal hypoglycemia, which may have serious consequences because it may not awaken the patient and is less likely to be observed by others [23]. A pooled analysis of data from five randomized controlled trials, involving a total of 2695 patients with inadequate control of type 2 diabetes on oral hypoglycemic medications alone, suggests that the addition of insulin glargine results in greater improvements in HbA1c ($p < 0.001$) and fasting blood glucose ($p < 0.001$) levels compared with NPH insulin in patients aged ≥65 years, whereas in younger patients (<65 years) similar glycemic improvements were observed with the two types of insulin [24]. When converting patients from a once-daily NPH regimen, common practice would be to reduce the insulin analog dose by 20% to ensure patient safety. Insulin detemir confers a weight advantage over glargine or NPH. Ultra-long-acting basal insulins such as degludec insulin may present an even lower risk of hypoglycemia, which would be especially advantageous in elderly patients. Insulin degludec incorporates structural modifications that allow it to form soluble and stable multi-hexamers [25]. Gradual separation of the monomers from the multi-hexamers following subcutaneous injection results in a continuous delivery of insulin into the circulation. Insulin degludec demonstrates a flat and stable glucose-lowering effect with once-daily administration [25]. The smoother pharmacokinetic and pharmacodynamic profiles of degludec insulin may reduce the frequency and magnitude of blood glucose troughs, thereby reducing the frequency and severity of hypoglycemic episodes. It has been shown that insulin degludec achieves glycemic control that is comparable to, or better than, that of insulin glargine with significantly lower rates of overall or nocturnal hypoglycemia [26].

22.8.2 Basal-bolus insulin regimen

A basal insulin regimen is considered non-physiological because it does not mimic normal insulin secretion, which consists of both basal and prandial insulin release as a basal insulin regimen administered at bedtime will be able to ameliorate the nocturnal hepatic glucose production but it may not be able to sustain blood glucose reduction throughout the day, especially after meals. Although many older people with type 2 diabetes will do well with this non-physiological regimen it is inappropriate for those with type 1 diabetes with endogenous insulin deficiency and some type 2 diabetes patients because of the progressive diminution in their insulin secretory capacity. There will therefore be a need to consider adding prandial or mealtime insulin coverage when persistent postprandial glucose excursions (e.g. blood glucose > 10 mmol/l) occur. This is suggested when the basal insulin regimen reaches its maximum potential as manifested by fasting blood glucose at its target but the HbA1c remains above goal after basal insulin up-titration (indicating that there is no room for a further increase in the basal insulin dose). The same would apply if hypoglycemia occurs during early morning hours or in between meals while titrating up the basal insulin. The aim with mealtime insulin is to blunt postprandial glycemic excursions. Practically, bolus insulin should be introduced meal by meal. For example, bolus fast-acting insulin can be added once daily before the meal responsible for the largest glucose excursion, subsequently a second injection can be administered before the meal with the next largest excursion, and ultimately a third injection can be added before the last meal. Another way of adding bolus insulin can be guided by the pre-meal blood glucose level. For example, insulin can be added before breakfast if the pre-lunch glucose level is elevated, or before lunch if the pre-dinner blood glucose level is elevated, or before dinner if the bedtime blood glucose level is elevated or a combination of these (Figure 22.1). Starting doses of about 10% of the total basal insulin dose before each meal but no more than 4–6 U is a reasonable start. Switching from basal to basal-bolus regimen will eventually require the total insulin dose unchanged, or slightly reduced to avoid hypoglycemia, but divided by about 50% basal and 50% bolus. For example, in a patient on 60 units of basal insulin the regimen could be changed to 30 units of basal and 8–10 units of fast-acting insulin before each meal as the bolus component. Further adjustments of the insulin dosage can be made according to the results of glucose monitoring before each meal and at bedtime. Such a basal-bolus regimen is the most restrictive for patients as they may need up to four injections daily and matching of pre-meal dose to calorie consumption. It may be appropriate for some well-functioning older individuals but when used as a simple regimen as possible should be adopted, with avoidance of strict carbohydrate counting or difficult dose adjustments. Both rapid-acting insulin analogs and short-acting regular insulins are reasonable choices for this regimen. However, rapid-acting insulin analogs mimic physiologic insulin secretion more closely than short-acting ones. When compared with human regular insulins, the rapid-acting insulin analogs such as aspart, glulisine, and lispro are more rapidly absorbed and have an earlier peak and shorter duration of action (onset within 15 min, peak at 60–90 min, and duration of 3–5 h). The rapid-acting insulin analogs can therefore be dosed at mealtimes, providing greater flexibility, while short-acting regular insulin (onset within 15–60 min, peak at 2–4 h, and duration of 5–8 h) should be dosed 30 min before a meal. Rapid-acting insulin analogs have a more rapid offset of action, resulting in a lower risk of hypoglycemia. Their use appears to be associated with better metabolic control and treatment satisfaction than regular human insulin [27]. A meta-analysis of rapid-acting analogs demonstrated better postprandial glycemic control and a mean 0.4% lower HbA1c when compared with human regular insulin [28]. There are no clinical differences in glycemic control or hypoglycemia risk between the three rapid-acting insulin analogs.

22.8.3 Premixed insulin regimen

Premixed insulin consists of a fixed combination of intermediate-acting insulin and regular insulin or a rapid analog. Premixed insulin offers an alternative to basal-bolus therapy for individuals who require basal and prandial insulin coverage. This regimen is somewhat inflexible but may be appropriate for certain patients who eat regularly and may be in need of a simpler approach than the basal-bolus regimen. This regimen is usually administered twice daily before morning and evening meals, but it can be given once, twice or three times daily depending on the needs of the individual. It can be taken initially before the largest

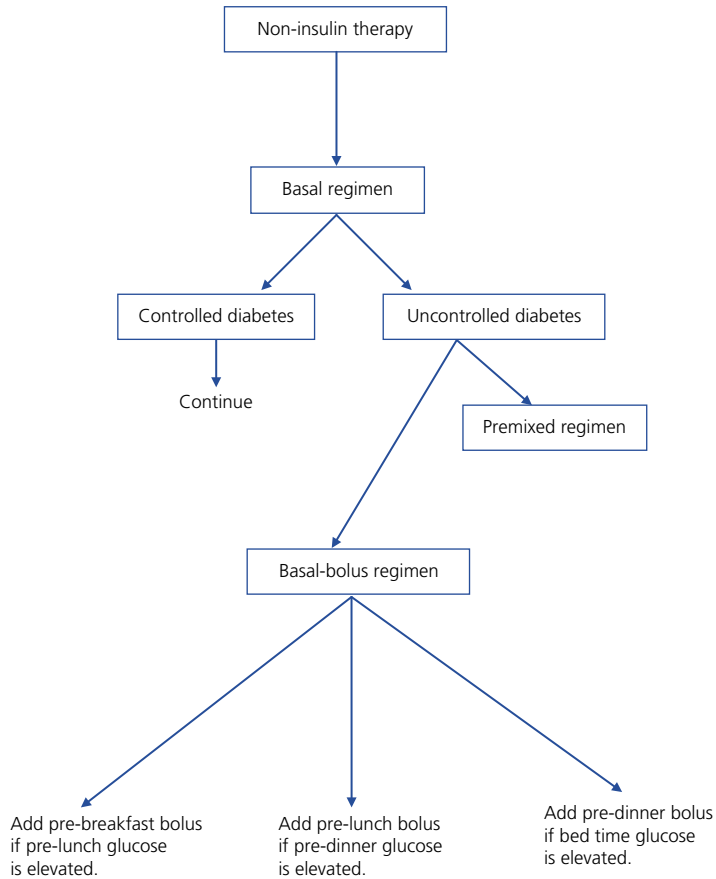

Figure 22.1 Initiation of insulin regimens in older people with diabetes.

meal, then at a second meal for twice-daily therapy, or with a third meal if greater control is needed. In general, when compared with basal insulin alone, premixed regimens tend to lower HbA1c to a larger degree, but often at the expense of slightly more hypoglycemia and weight gain [29]. Another disadvantage is less flexibility in titrating up the shorter from the longer-acting component of these formulations. The simplicity of the premixed insulin makes it easier to use in patients with vision difficulty or dexterity issues, and to avoid any potential mistakes made during mixing of long- and short-acting insulin in the basal-bolus regimen. However, it is important to remember that a regular eating pattern is needed when using premixed insulin and the doses should always be given before meals. Premixed NPH and regular insulin as well as rapid-acting insulin analogs mixed with their intermediate acting protamine suspension provide dual fasting and postprandial glycemic control with fewer injections. Similar to basal and rapid-acting analogs, analog premixed insulins offer advantages over human premixes as they exhibit more physiological action profiles with faster onset of action, more consistent duration of therapy, better postprandial glycemic control, more convenient dosing, and reduced risk of hypoglycemia. Different regimens are compared in Table 22.1.

22.9 Insulin therapy in care homes

The prevalence of diabetes in care homes is high, affecting around 25% of long-term healthcare facility residents in the USA [30]. Residents with diabetes in care homes also suffer a higher co-morbidity burden than individuals without diabetes. For example, residents with diabetes in US care homes have an average of 6.4 major diagnoses compared to only 2.4 for those without the disease [31]. These patients represent a

Table 22.1 Comparison between insulin regimens.

	Basal regimen	Basal-bolus regimen	Premixed regimen
Indication	First choice regimen given once daily at bed time	When basal regimen fails with persistent post-prandial glucose excursions	When basal regimen fails with persistent post-prandial glucose excursions
Advantages	Simple, once daily, easy titration, less hypoglycemia and weight gain risk	More physiologic, good glycemic control	Simple, fixed doses, good glycemic control
Disadvantages	Less physiologic with post prandial glucose excursions	Complex titration, frequent injections, high risk of weight gain and hypoglycemia	Inflexible titration, high risk of weight gain and hypoglycemia, needs regular eating pattern
Suitable population	All elderly, convenient in patients with relaxed targets	Patients with good physical and cognitive function and those aiming tight targets	Well-functioning patients, those with predictable eating pattern and those aiming tight targets
Titration	Guided by fasting blood glucose	Bolus doses are guided by 2 h post-prandial excursions or pre-meals and bed time blood glucose Basal dose guided by fasting blood glucose	Morning dose guided by previous pre-dinner blood glucose Evening dose guided by fasting blood glucose

complex, high-risk group and require an individualized approach to diabetes care. Although the principles of insulin therapy are the same as in older people living in the community, clinical priorities and strategies must be tailored to the individual and glycemic goals balanced against quality of life. Tight glycemic control is inappropriate in this population but good glycemic control to alleviate symptoms and acute complications due to hyperglycemia, such as infections, incontinence, dehydration, confusion and hospitalization without inducing hypoglycemia, is appropriate. Patients in care homes are likely to be older, with longer duration of diabetes, which may be associated with defective glucose counter-regulation, leading to increased risk of hypoglycemia and hypoglycemia unawareness. Extra caution should therefore be taken when initiating insulin therapy. For example, regular insulin should not be used due to its longer duration of action compared to the rapid-acting analog insulin, which may increase the risk of hypoglycemia occurring between meals. Insulin administration using a sliding scale should also be avoided in these settings due to increased frequency of finger sticks and reduced quality of life. Sliding-scale insulin refers to the subcutaneous administration of short- or rapid-acting insulin based on a certain threshold of hyperglycemia assessed using finger-stick blood glucose measurement. Basal insulin is not typically administered as part of a sliding scale, which can result in high blood glucose each morning. Sliding-scale regimens therefore do not provide a physiological approach to insulin therapy. A sliding-scale regimen also leads to unpredictable fluctuations in blood glucose levels because it retrospectively treats hyperglycemia rather than preventing it and is associated with poor glycemic control. In a retrospective study in US care homes of 2096 residents, mean (SD) age 74 (12.1) years, with type 2 diabetes treated with insulin, 73.8% of participants received a sliding-scale insulin regimen. Participants treated using a sliding scale were more likely to be younger (p = 0.01), non-white (p = 0.002), and receiving sulfonylurea (p = 0.004) than non-sliding-scale-treated participants. The sliding-scale regimen was associated with a mean (SD) 19.9 (7.9) finger sticks per week, of which 12.5 (7.6) were not followed by insulin administration. Fewer participants on the sliding-scale regimen had one or more HbA1c measurements of 7.0% or less (48.8% vs 57.2%) or 8.5% or less (85.2% vs 87.6%, respectively) compared to non-sliding-scale-treated participants. Rates of hypoglycemia were similar in both groups (15% vs 14.9%). This high finger-stick burden translates into a compromised quality of life because blood glucose levels are monitored frequently and numerous insulin injections are given, thus increasing discomfort [32]. More importantly, targets in care home residents with diabetes should focus on short-term day-to-day blood glucose levels rather than on a long-term HbA1c value due to

the limited life expectancy of this population. Short-term targets in a comfortable daily range of random blood glucose (>4 but <15 mmol/l) is appropriate as blood glucose outside this range is likely to be symptomatic and results in cognitive changes [13].

22.10 Insulin therapy in diabetic patients with dementia

Older people on insulin therapy should be able to inject themselves, self-monitor blood glucose levels, adjust insulin doses and be able to recognize and manage hypoglycemia. However, diabetes is associated with a significantly increased risk of cognitive decline and dementia [33]. Older people with diabetes and dementia may not be able to self-administer insulin, which may lead to poor glycemic control, dosing errors, and increased risk of hypoglycemia [34]. It is not known what degree of cognitive function is necessary for diabetic patients to correctly self-inject insulin, therefore older people with diabetes should be screened periodically for signs suggestive of cognitive impairment (Box 22.5). The 1-min mental status examination for category fluency (inquiring about the patient's name, and asking him or her to list as many different animals as possible in 1 min) [35] has been recently shown in a cohort of 278 patients with diabetes and receiving insulin therapy, mean (SD) age 75.3 (5.9), to be more useful than the mini-mental state examination to evaluate the reliability of insulin self-injection [36]. A 1-min mental status examination score of ≤10 predicted insulin self-injection to be "impossible", with a sensitivity of 65.6% and a specificity of 69%. It has been shown that about a quarter of older people with diabetes and using insulin are already cognitively impaired [37]. Individuals with cognitive impairment using insulin were significantly more likely not to know what to do in the event of hypoglycemia and gave more incorrect responses when asked about diabetes mellitus management than those who are cognitively intact [37]. These patients should therefore be closely monitored and supported by carers to supervise insulin administration. For example, basal long-acting insulin analogs are simple to use and in patients with an erratic eating pattern rapid-acting insulin analogs can be given either during or immediately after meals to control prandial glucose excursions. If such a patient does not eat adequate carbohydrates, then the dose of the insulin can be adjusted down or omitted altogether to avoid inducing hypoglycemia.

Box 22.5 Signs suggestive of cognitive impairment in older people with diabetes.

Clinician should suspect cognitive impairment if one of the following occurs:

- patient forgets to take medications regularly
- patient forgets to inject him/herself with insulin
- patient forgets how to treat hypoglycemia
- recurrent unexplained hypoglycemia
- patient is unable to interpret blood glucose results or make decisions regarding adjusting insulin doses
- patient is non-compliant with self-care
- patient is non-compliant with dietary requirements
- patient has an erratic eating pattern and misses meals

22.11 Insulin therapy in tube feeding

In older patients fed by the enteral route, the management of hyperglycemia is aimed at the maintenance of blood glucose within an acceptable range whilst limiting the risk of hypoglycemia. Risk of hypoglycemia is high during the rest period between feeds, while the patient is receiving no food at all, thus close monitoring of the patient is recommended. Patients on enteral feed can be managed fully by the administration of a subcutaneous insulin regimen without the need for the intravenous route. For patients on a continuous enteral feed, a premixed insulin regimen can be used with the first dose administered at the start of the feed and the second dose at the midpoint of the feed. The whole dose of insulin can be divided equally between the two doses. Alternatively, a basal insulin regimen can be used alone, administered at the start of the feed. A basal-bolus regimen can be used if persistent hyperglycemia occurs despite a basal regimen (blood glucose >12 mmol/l) with the basal insulin given at the start of the feed and a bolus of rapid-acting insulin analog administered at 6 and 12 h into the feed. This regimen is of particular use for people with type 1 diabetes. For patients on bolus feeding, single doses of rapid-acting insulin analog can be given 15 min prior to the administration of each bolus feed. As the feed rate and

volume increase, the subcutaneous insulin dose will need to be increased by about 10–20% per titration. Basal insulin should be continued for those with type 1 diabetes or those with type 2 diabetes already on basal insulin. A target fasting (pre-feed) glucose range of 5–8 mmol/l and random (feed) glucose of 6–12 mmol/l is appropriate for the management of diabetes during enteral feeding to reduce the risk of hypoglycemia. Continuation of metformin (in suspension form through the enteral tube) is useful but crushing of oral tablet medications for administration through the tube is not recommended given the unpredictable absorption, difficulties in administration, and the risk of tube blockage with crushed debris. When the feed is stopped unexpectedly, patients with type 1 diabetes should not have their insulin omitted and their blood glucose should be monitored closely to avoid hypoglycemia. In this case basal insulin is continued in addition to variable dose intravenous insulin, if needed, to keep blood glucose in the range of 6–12 mmol/l. For patients with type 2 diabetes, insulin can be temporarily stopped with close monitoring of their blood glucose and insulin re-administered if hyperglycemia occurs. Nursing staff looking after these patients should be trained in blood glucose monitoring in addition to recognition and treatment of hypoglycemia.

22.12 Special considerations

Older people with diabetes have high rates of functional disability, chronic diseases, ill-health, and risk of having geriatric syndromes, including depression, urinary incontinence, chronic pain, and frailty causing cognitive impairment and frequent falls [38] (Box 22.6). Age-related changes in functional ability and senses will affect patients' ability to administer insulin, monitor blood glucose, and manage hypoglycemia. Social isolation is another factor leading to more dependency on carers, therefore the approach to insulin therapy in older patients with diabetes requires special considerations.

22.12.1 Reducing hypoglycemia

Hypoglycemia is the key rate-limiting step for optimizing glycemic control. It is more common in old age due to impaired renal and hepatic function, slow glucose counter regulatory hormone secretion, polypharmacy, and erratic or poor food intake [39]. In addition to the serious consequences of hypoglycemia, such as myocardial infarctions or cardiac arrhythmias, in the elderly, it may affect the quality of life as a result of the associated symptoms, which can lead to fear of future episodes, anxiety, and greater burden on carers, therefore the greater risk of hypoglycemia in this age group must be considered when starting insulin. Use of insulin analogs, rather than human insulins, reduces risk of hypoglycemia. Risk factors for hypoglycemia should be reviewed and monitored periodically [12] (Box 22.7). The risk of hypoglycemia can be reduced by addressing these factors. Strategies for preventing hypoglycemia in patients using insulin include asking about hypoglycemia at each visit, continuous education, and continued professional support. Capillary glucose should be tested twice daily initially when insulin is introduced and dosage is gradually increased. After stabilization a four-point profile twice a week is appropriate. Monitoring should be stepped up during acute illness or when hypoglycemia is suspected. Hypoglycemia can also occur during the night while asleep (nocturnal hypoglycemia), with various patient reactions such as wakening up from sleep, having vivid dreams or causing sweating and confusion. On some occasions patients may sleep through the nocturnal hypoglycemic episode and wake up in the following morning with headache or hangover sensation. Carers and patients should be educated to recognize these symptoms. Carers may need to recognize that if patients become restless or noisy during sleep they may be having nocturnal hypoglycemia and advised to wake patients up get their blood glucose checked.

Box 22.6 Common conditions in older people with diabetes.

- Multiple co-morbidities
- Physical dysfunction
- Cognitive dysfunction
- Depression
- Falls and fractures
- Frailty
- Polypharmacy
- Urinary incontinence
- Visual and hearing impairment
- Chronic pain
- Irregular eating pattern
- Nutritional need and hydration
- Vulnerability to hypoglycemia

Box 22.7 Risk factors for hypoglycemia in older people with diabetes.

- Old age
- Hypoglycemia unawareness
- History of hypoglycemia
- Long duration of insulin therapy
- Long duration of diabetes
- Combination of insulin with sulfonylurea therapy
- Erratic food intake or missed meals
- Cognitive dysfunction
- Depression
- Social isolation
- Excess alcohol use
- Frailty
- Renal or hepatic impairment
- Polypharmacy
- Sepsis
- Endocrine deficiencies, for example adrenal, pituitary or thyroid deficiency
- Disseminated malignancy

22.12.2 Improving compliance

The initiation of insulin therapy in older people with diabetes should be user-friendly, with minimal lifestyle disruption to improve compliance. For example, poor dexterity, poor vision or cognitive dysfunction may limit effective insulin administration. The use of insulin delivery devices that provide effective glycemic control while simplifying administration can be of particular value. In these instances, insulin pen devices may facilitate insulin use [40]. They are more accurate, more portable, and more compact than traditional vials and syringes. They are also simple to learn how to use, easy to self-titrate, and may help patients to adapt to and accept insulin therapy. Pens may also improve quality of life by reducing the risk of hypoglycemia due to dosing errors with the vials and syringes devices. Initiating or switching to a disposable pen is associated with better treatment persistence and adherence than initiating or continuing with vial and syringe without increased total healthcare costs. Among insulin-naïve patients, initiating insulin by disposable pen was also associated with a significantly reduced risk of hypoglycemia compared with vial and syringe patients [41]. Such improvements may result in improved clinical and economic outcomes, with a reduction in all-cause and diabetes-related hospitalizations among pen initiators [41]. Schwartz *et al.* also reported that 88% of patients found the insulin pen device to be more reliable in drawing and dispensing insulin, and there was also a significant reduction in administration time ($p < 0.05$) compared to vial and syringe injections [42]. The use of insulin analogs with the simplest insulin therapy regimen that achieves the desirable glycemic target with minimal risk of hypoglycemia or undesirable weight gain may improve patients' compliance. It is also important to help patients overcome barriers including fear of injection pain, public embarrassment, and hypoglycemia risk.

22.12.3 Education and multidisciplinary care

Insulin treatment will fail if the patient or carers cannot cope with the injections or if hypoglycemia is troublesome. Older people with diabetes should be educated about insulin therapy, especially the recognition of hypoglycemia symptoms and appropriate insulin dose adjustments when hypoglycemia occurs. The outcomes and clinical implications of insulin therapy should be communicated in an easy and understandable way. Carers should also be included in a comprehensive diabetes mellitus education program as part of the treatment plan. There may be a need to change patients' negative beliefs and perceptions about insulin therapy. Every effort must be made to help patients to understand the progressive nature of diabetes and that the need for advancing therapy only reflects a disease state but not a personal failure. Patients should also be informed that insulin therapy is associated with general wellbeing and improved quality of life. A systematic and multidisciplinary team approach to care with a focus on providing patients with support to cope with their disease will help to improve outcome. The use of outcome and process indicators to measure performance of care systems is appropriate. Support from formal and informal carers, social services, and voluntary agencies may have to be increased gradually as patients age and the disease progresses. All patients in care homes should have a structured care plan with a regular review of the goals of therapy and the educational needs of carers.

22.12.4 Insulin resistance and pump therapy

For selected patients with severe insulin resistance, regular insulin (U-500) is more effective alternative to U-100 insulin. U-500 regular insulin has a pharmacokinetic profile similar to NPH. It more effectively controls

hyperglycemia at a lower cost per unit of insulin than U-100 insulin in severely insulin-resistant patients. Continuous insulin infusion using an external pump is an alternative to a basal-bolus regimen. It has similar efficacy in improving glycemic control and hypoglycemic risk when compared with multiple insulin injections in patients with type 2 diabetes [43]. However, in adult type 1 diabetes continuous subcutaneous insulin infusion via a personal pump was more effective than multiple daily injections and appeared to be safe regardless of age [44]. This regimen, however, should be reserved for those of younger age with a longer life expectancy, a shorter duration of diabetes, and little or no end organ complications.

22.12.5 Insulin withdrawal

In patients who continue with insulin, the glycemic goals and regimen should be reviewed with aging, especially with the onset of cognitive impairment or frailty. Declining body function associated with weight loss, malnutrition, and frailty may lead to reduced body needs of hypoglycemic medications, including insulin, with a resultant increased risk of hypoglycemia. Insulin therapy can therefore be titrated down or completely stopped in those populations who have significant weight loss, frailty or recurrent serious hypoglycemic episodes. Hypoglycemic medications have been safely withdrawn in a cohort of frail nursing home older patients with diabetes, mean (SD) age 84.4 (6.8) years [45], and in another group of older patients in the community, mean (SD) age 86.5 (3.2) years, attending an outpatient clinic without deterioration of their glycemic control [46]. The main characteristics of patients at the point of hypoglycemic medication withdrawal were significant weight loss, increased co-morbidities, including dementia, and polypharmacy with recurrent hypoglycemia [46]. Patients with these criteria therefore appear to be suitable candidates for a trial of insulin withdrawal. This may reduce the risk of hypoglycemia and a periodic review of insulin therapy in these patients is recommended.

22.13 Conclusion

Insulin therapy is frequently required during the course of diabetes mellitus treatment due to the progressive loss of β-cell mass and function, therefore insulin therapy should be considered in patient counseling from the outset. While insulin is effective for all patients with diabetes, insulin is underutilized in older people due to concerns about hypoglycemia and complexity of administration. However, early use of insulin therapy in the elderly may be useful because of the high frequency of co-morbidities with associated renal or hepatic impairment that may preclude the use of many oral hypoglycemic medications. The simplest and most convenient way to initiate insulin is the addition of basal insulin to existing oral hypoglycemic medications if appropriate, once daily at bed time to suppress nocturnal hepatic glucose production. Although the majority of patients with type 2 diabetes requiring insulin therapy can be successfully treated with basal insulin alone, some, because of progressive diminution in their insulin secretory capacity, will require prandial insulin therapy. The options here are either to add a bolus short-acting insulin or switch from basal insulin to twice-daily premixed insulins. Premixed and basal-bolus regimens result in greater reductions in HbA1c compared to basal regimens but are associated with more weight gain and increased risk of hypoglycemia, and are more complex, which may affect compliance. Insulin analog formulations are superior to human insulins with respect to the risk of hypoglycemia, and the use of insulin pens improves compliance. The ultimate goal is to provide the patient with an individually tailored, flexible regimen that maintains health and quality of life.

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CHAPTER 23

Hypertension in older diabetic patients

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KEY MESSAGES

- The combination of elevated blood pressure and hyperglycemia has the highest population-attributable fraction of cardiovascular disease incidence and has a substantial effect on the development of further micro- or macrovascular complications.
- The etiology of hypertension in an older diabetic individual is likely to be multifactorial in origin.
- There is a strong association between rapidly changing lifestyle, an increase in sedentary profile, with limitation of physical inactivity, and development of hypertension and diabetes.
- The goals of treatment in hypertensive and diabetic older people are to control blood pressure within an acceptable range, reduce the risk of micro- and macrovascular complications, prevent orthostatic hypotension and resultant falls, avoid polypharmacy, ensure compliance and reduce side effects, and maintain functionality, independence, and autonomy.
- Among individuals older than 60 years of age a goal of 150/90 mmHg is generally considered acceptable. For diabetic individuals blood pressure should be lowered to a target of 140/90 mmHg since controlling the blood pressure to a lower level has been shown to further prevent micro- and macrovascular complications.

23.1 Introduction and background

The prevalence of diabetes and hypertension has been increasing worldwide over the last few decades. It has been estimated that almost 40–60% of diabetic individuals also suffer from hypertension [1]. The coexistence of diabetes and hypertension varies with ethnic, social, and racial diversities. Together they account for limitation of functional ability and result in the decline in quality of life of an individual. The combination of elevated blood pressure and hyperglycemia has the highest population-attributable fraction of cardiovascular disease incidence and has a substantial effect on the development of further micro- or macrovascular complications [2]. This creates a huge economic burden in terms of therapy, monitoring issues, and managing associated complications, disabilities, and co-morbidities.

Physiologically, aging leads to a state of insulin deficiency and results in insulin resistance. It causes stiffness of blood vessels and other atheromatous changes in the cardiovascular system. Hypertension and diabetes have become a part of aging. It has been reported that the prevalence of hypertension in the diabetic population rises from 40% at the age of 45 years to 60% at 75 years [3]. Older individuals who are both diabetic and hypertensive have higher rates of premature deaths, functional disability, and coexisting cardiovascular diseases.

The etiology of hypertension in an older diabetic individual could be multifactorial in origin. There is a strong association between rapidly changing lifestyle, increase in sedentary profiles, limitation of physical inactivity, and development of these chronic conditions. In addition obesity and the metabolic syndrome play a crucial part in their genesis.

Older individuals also require special attention in view of other co-morbidities and geriatric syndromes such as polypharmacy, cognitive impairment, urinary and bowel incontinence, somatic pains, and frequent falls.

Diabetes in Old Age, Fourth Edition. Edited by Alan J. Sinclair, Trisha Dunning, Leocadio Rodríguez Mañas, and Medha Munshi.

It has been established that prompt diabetic management in hypertensive patients and lowering of blood pressure in diabetic patients results in a decline in morbidity and mortality [4, 5]. However, the finer aspects of management among these patients remain ambiguous. There are several challenges not only at the level of an individual patient but also at provider and system level. Treatment safety, quantification and qualification of physical activity, diet planning, calorie requirements, frequent hypoglycemia, and prevention of complications need to be addressed. Although it is believed that the patient-centered specialist care approach is optimal, management requires careful consideration of the effects of advancing age, changes in health status, and patient-tailored therapeutic interventions with constant supervision and monitoring.

23.2 Prevalence and impact

According to World Health Organization, the prevalence of diabetes in adults is predicted to rise by 5.4% and there will be 300 million affected individuals by 2025 [6]. The International Diabetes Federation (IDF) also estimates that 366 million diabetic individuals in 2011 will increase to 552 million by 2030 [7]. The IDF estimates the global prevalence of diabetes in people between 60 and 79 to be 18.6% [7]. Similarly, the number of hypertensive individuals has also been projected to increase by 60% to a total of 1.56 billion by 2025. Approximately 70% diabetic patients are also hypertensive [2]. Extrapolating these estimates, it follows that by the third decade of this century nearly 200 million people will be suffering from hypertension and diabetes together. Furthermore, diabetes has been indicted in as many as 10% of deaths attributed to hypertension-related disease [8].

23.3 Normal blood pressure and the definition of hypertension

There is a slight variability in the definition of hypertension in older individuals as proposed by several contemporary guidelines, although most warn against very aggressive and tight control in this group. Most guidelines advocate a specific blood pressure goal to achieve of between 130 and 140/80-90 mm Hg, beyond which an increase in morbidity and mortality is expected. Over the past few decades, the framework for disease quantification has been evolving rapidly. Nearly two decades ago, the normal systolic blood pressure was defined by the simple formula of "100 plus age" and this was propagated as a straightforward memory aid [9, 10]. A study conducted at the University of California, Los Angles in 2000 suggested another uncomplicated formula to determine normal blood pressure for men of 110 + (2/3 of chronological age) and for women as 104 + (5/6 of chronological age) [11]. Normal blood pressure was viewed as a dynamic continuum changing with the age of the patient until the last century. However, accumulating evidence has resulted in a radical modification in this approach and fixed cut-off measures have been aggressively advocated in recent years, resulting in the inclusion of more and more individuals under the treatment umbrella.

According to the guidelines of the National Institute of Health and Care Excellence (NICE) released in 2011, blood pressure when measured in a clinic setting as more than or equal to 140/90 mm Hg or an ambulatory or home blood pressure recording of more than or equal to 135/85 mm Hg is labelled stage 1 hypertension. NICE further categorized blood pressure as stage 2 (more than 159/99 mm Hg) and severe hypertension (more than 179/109 mm Hg) [12].

The guidelines of the European Society of Hypertension (ESH) published in 2013 advocated a similar grading but they specified normal (120–129/80–84 mm Hg) and high normal (130–139/85–89 mmHg) ranges. Furthermore, they advocated that pre-hypertension or high normal is an important stage at which intervention could prevent further co-morbidities [13].

The guidelines of the 7th Joint National Committee (JNC 7) advocated that blood pressure in diabetic older people should be lowered to at least 130/80 mm Hg [14]. Pre-hypertension was defined as a blood pressure between 120/80 and 129/89 mm Hg. Recently, the guidelines of the 8th Joint National Committee (JNC 8) published in 2014 classified blood pressure according to age and other co-morbidities [15]. This guideline does not specify the stages but emphasizes treatment goals according to specified age groups. Among older hypertensives, the JNC advocates a blood pressure of 150/90 as a goal for therapy but redefined this to 140/90 for hypertensive older diabetics.

23.4 Hypertension in diabetic older persons

Hypertension in elderly diabetics is a distinctive phenomenon and requires special attention not only because the needs of older people are different but also because there are further distinctive features in the behavior and presentation of illness between elderly and very elderly individuals. An older patient with hypertension and diabetes could have a long history with either or both of these conditions with or without associated complications. An older patient who is detected for the first time to have either diabetes or hypertension could have harbored these conditions for a longer period, remained previously undiagnosed, and may have masked or unmasked complications at the time of detection. On the other hand, an older patient who is detected for the first time to be hypertensive or diabetic may have a truly new onset of disease with its own unique pathophysiology.

Presentation and progression also vary with other co-morbidities and chronic illnesses associated with aging. It has been observed that most people who present before 50 years of age have predominantly diastolic hypertension whereas those who are over 50 years are more prone to get isolated systolic hypertension [16]. Isolated systolic hypertension further predisposes to cardiovascular diseases and other diabetic complications [17].

Diabetes is a state of hyperinsulinemia that stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone-system (RAAS), which can cause vascular damage [18, 19]. Insulin resistance leads to impaired insulin signaling that stimulates late mitogenic signal pathway, which increases smooth muscle proliferation [19, 20]. The vascular damage leads to further worsening of hypertension through sodium retention and resultant volume expansion in older people because their body compensation is also compromised. Hyperglycemia can damage not only kidneys but also arterial walls through deposition of advanced glycation end (AGE) products, generation of reactive oxygen species (ROS), and activation of protein kinase C [18, 19]. It also leads to increased vascular inflammation (over-expression of interleukin 6 (IL6), vascular cellular adhesion molecule-1 (VCAM1), and monocyte chemo-attractant protein) [19, 20]. Diabetes leads to an increase in coagulation factors, which in turn promotes plaque progression [8, 19]. It also decreases the level of antithrombin III (AT III) and protein C, which further impairs fibrinolysis. Diabetes and hypertension in combination have been proposed to impair ventricular myocyte relaxation [19, 21].

23.5 Measurement of blood pressure

The correct method to measure blood pressure should be employed while making the diagnosis of hypertension. This assumes further importance in older patients since they are also prone to developing white-coat hypertension or isolates systolic hypertension, which could be missed unless the physician is aware and sensitive to their occurrence. Attention should be paid to not only to the procedure of measurement but also the type of blood pressure instrument used. The patient should be made to sit in a chair with the back rested and arms bared, and supported at the level of the heart. Before measuring blood pressure the patient should refrain from smoking, ingestion of caffeine, and vigorous exercise for at least 30 min. It is also important to use the appropriate size of blood pressure cuff with reference to the age and weight of patient. The bladder of the sphygmomanometer cuff should encircle 80% of the upper-arm circumference and cover at least 40% of its length. Although well-calibrated mercury sphygmomanometers are ideal, with the rise in popularity of automated machines their availability has declined in recent times. Automated instruments should be carefully and regularly calibrated to ensure reliability. Systolic and diastolic blood pressure should be noted with the first appearance and disappearance of Korotkoff sounds, respectively. At least two readings 2 min apart should be measured and if the difference between the two readings is more than 5 mm Hg, a third reading should be taken [4]. An average of the two higher readings should be used to guide decisions on therapy. If there is a significant difference in the individual blood pressure recordings then the entire process should be repeated after a short interval [22].

23.6 Goals of management

The goals of treatment in hypertensive and diabetic older people are the following:

1. Control blood pressure within an acceptable range.
2. Reduce the risk of micro- and macrovascular complications.

3 Prevent orthostatic hypotension and resultant falls.
4 Avoid polypharmacy, ensure compliance, and reduce side effects.
5 Maintain functionality, independence, and autonomy.

23.6.1 Control of blood pressure within an acceptable range

Almost all guidelines for the management of hypertension support relaxation in goals for blood pressure control in older individuals. Among individuals older than 60 years of age a goal of 150/90 mmHg is generally considered acceptable [15]. For diabetic individuals blood pressure should be lowered to a target of 140/90 mmHg, since controlling the blood pressure to a lower level has been shown to further prevent micro- and macrovascular complications. A more aggressive approach towards tighter control with lower targets is often counterproductive and an inverse relation has been noticed between mortality and blood pressure levels.

23.6.2 Reduce the risk of micro- and macrovascular complications due to hypertension and diabetes

The UK Prospective Diabetes Study (UKPDS) established that each 10 mmHg decrease in mean systolic blood pressure was associated with a 12% risk reduction for any diabetes-related complication. In addition to this, there is a reduction of 15% in diabetes-related deaths, 11% in myocardial infarctions, and 13% in microvascular complications [23]. The UKPDS and Hypertension Optimum Trial (HOT) showed that early treatment of blood pressure and its tight control lead to significant reduction in microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, stroke, and peripheral vascular disease) complications. The trials like the Systolic Hypertension in Elderly Patients (SHEP) trail, the Systolic Hypertension Europe (SYST-EUR) trail, and HOT have confirmed that reduction in cardiovascular risk is achieved with tight blood pressure control, and the beneficial effect is up to three-fold when the patient is both diabetic and hypertensive.

23.6.3 Prevent orthostatic hypotension and resultant falls

Advancing age and the presence of diabetes together make patients more prone to develop autonomic dysfunction and orthostatic hypotension. This needs special attention as it can cause spurious high blood pressure recordings, leading to over-medication and further aggravating the problem. It also leads to frequent falls and preventable resultant morbidity.

23.6.4 Avoid polypharmacy, ensure compliance, and reduce side effects

Older patients are likely to visit several specialists in the course of their illness and receive multiple prescriptions, often leading to polypharmacy. This not only renders them vulnerable to potentially harmful drug interactions but also exposes them to over-dosing and side effects. Polypharmacy is also responsible for an increased pill burden and reduced compliance with essential medications. The control of hypertension and diabetes both rely on adherence to therapy and behavioral modification. A simple but careful review of prescriptions at each visit reduces the pill burden and improves compliance, thereby improving control while minimizing side effects.

23.6.5 Maintain functionality, independence, and autonomy

Maintaining a functional and active life during aging and promoting autonomy is extremely important but often ignored. Dependence on formal or informal caregivers leads to increased chances of abuse, thus triggering a vicious cycle leading to a further decline in functionality and health. Maintaining functionality for longer periods improves life satisfaction and productivity. It is essential to include older patients in the decision-making process not only to improve compliance but also promote quality of life.

23.7 Initiation of therapy

A large number of patients will have either an already established hypertension or diabetes or both when visiting the geriatrician for the first time. A careful review and revision of all previous prescriptions should be made at this visit. In addition, it is imperative to physically verify and visually review all the pills and drugs being actually consumed by the patient.

When high blood pressure is detected for the first time during a visit by an older patient, screening should include the patient's medical history to firmly establish the onset and duration of hypertension and a thorough attempt should be made to identify complications and other associated co-morbidities. A comprehensive

geriatric assessment and evaluation is essential prior to initiation of therapy. All individuals should be carefully examined for peripheral neuropathy, signs of autonomic neuropathy, and other cardiovascular complications. Supportive laboratory examination should be an integral part of the patient's initial evaluation [24].

23.8 Non-pharmacological management

Early detection and prompt intervention can prevent morbidity and mortality in older diabetics [22]. It also decreases the further healthcare burden on society for dependent individuals.

23.8.1 Exercise and regular physical activity

Lower levels of physical activity are especially likely in the population at risk for diabetes and hypertension, and exercise has become a central strategy in both diabetes prevention and management. Exercise improves glycemic control and body fitness. Progressive decline in fitness, muscle mass, and strength with aging is in part preventable by regular exercise [25]. The decrease in insulin sensitivity with aging is also partly attributable to lack of physical activity [5, 25]. The physical activity should be designed to maintain an ideal body mass index (BMI) to reduce risk of complications. Around 150 min/week of physical activity produces the required benefit [1, 15, 25]. Vigorous aerobic exercises combined with anaerobic or resistance exercise should be tailored to individual patient needs. Limited exercise is advocated depending on individual tolerance and capacity in frail, dependent, delirious patients or those with frequent hypoglycemia, peripheral neuropathy, autonomic dysfunction, osteoarthritis, foot lesions, proliferative retinopathy, and peripheral vascular disease [26]. The exercise plan could be split into two or three fragments in a day, starting with 5 min each, which should be progressively increased over a period of 2–3 weeks [25].

It is likely that maintaining better levels of fitness will lead to a reduced incidence of chronic vascular disease and an improved quality of life. A simple memory aid has been advised for physical activity: FITT stands for frequency (4–5 days per week), intensity (depending on the physical ability of the person), timing (30–40 min per day), and type of exercise (aerobic, anaerobic or resistance). It has been shown that progressive resistance exercise improves insulin sensitivity to the same extent as aerobic exercise in older men. At least two weekly sessions are recommended and each session should include one set of five or more resistance exercises involving large muscle groups.

23.8.2 Dietary modifications

Dietary restrictions in terms of calorie and sodium restraint are important in management. The dietary approach to stop hypertension (DASH) diet plan enables an older individual to lower blood pressure up to 11/5 mmHg [4]. The DASH diet was proposed not as a weight-reducing diet but to provide high fiber and low fat [27]. It includes low-calorie food substances and is designed to provide 2300 calories per day. It is high in potassium, calcium, and magnesium but low in sodium. Dietary requirements need to be individualized in patients who are frail, dependent, have frequent episodes of hypoglycemia or are receiving end-of-life care [7, 28]. A DASH diet plan is shown in Table 23.1.

The DASH diet was originally proposed for an adult population but older patients may require special considerations in terms of calorie requirement. It provides a useful and a handy reference to designing a healthy diet plan for older individuals. It is important to note that individuals aged 60–69 years require approximately 550 kcal less than an average adult per day and those between 70 and 79 years require 745 kcal less. An average older person requires 20–25 kcal/kg body weight every day [29]. The protein requirement increases with age and a deficit of up to 15% in malnourished individuals and 25–85% in long-term care facilities has been recorded. Suitable improvisations in the diet plan to allow for these requirements may be made to ensure adequate nutrition.

Most patients and healthcare workers remain uncertain about advice regarding salt intake. Patients are often advised to reduce salt or adopt a low-salt diet in generalist statements. This often aggravates patients' confusion, resulting in misinterpretation and reduced compliance. One teaspoon of table salt (approximately 6 g) contains 2300 mg of sodium. In the general population a salt reduction of less than 2300 mg per day is advocated. In patients with both hypertension and diabetes, a further reduction of up to 1500 mg per day may be beneficial. However, it is often difficult to

Table 23.1 DASH eating plan.

Food types	Daily servings (except when specified)	Serving size
Grains	7–8	1 slice bread 1 cup ready-to-eat cereal ½ cup cooked rice, pasta or cereal
Vegetables	4–5	1 cup raw leafy vegetable ½ cup cooked vegetable 6 ounces vegetable juice
Fruits	4–5	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen or canned fruit 6 ounces fruit juice
Low-fat or fat-free dairy products	2–3	8 ounces milk 1 cup yogurt 1½ ounces cheese
Lean meat, poultry, and fish	2 or fewer	3 ounces cooked lean meat Skinless poultry or fish
Nuts, dry fruits	4–5 per week	1/3 cup or 1½ ounces nuts 1 tablespoon or ½ ounce seeds ½ cup cooked dry beans
Fats and oils	2–3	1 teaspoon soft margarine 1 tablespoon low-fat mayonnaise 2 tablespoons light salad dressing 1 teaspoon vegetable oil
Sweets	5 per week	1 tablespoon sugar 1 tablespoon jelly or jam ½ ounce jelly beans 8 ounces lemonade

balance between palatability and adequate sodium reduction, and strict reduction may result in inadequate nutrition. A no-added salt diet implies that the person should not use any extra salt on table over and above what has been used in cooking. A low-salt diet in which salt is reduced at the time of cooking food restricts sodium consumption to levels lower than 1500 mg per day while a no-salt diet in which salt is neither used during cooking nor added to food on table brings the restriction to 200–300 mg [4, 30]. An average reduction of sodium of up to 1500 mg per day in the diet leads to lowering of blood pressure up to 5.1/2.7 mmHg [4]. Reducing sodium intake further disrupts the balance between decline in palatability and providing adequate nutrition. Ingestion of 80 mmol or more of potassium has been shown to be protective against hypertension. The role of calcium or magnesium in the management of hypertension remains to be elucidated.

Amino acid supplementation has also been advocated by some researchers to improve insulin sensitivity and control of blood sugar in older diabetic patients, especially in frail older subjects [31, 32].

23.8.3 Lifestyle changes

Smoking has remained an important risk factor and its contribution to the development of micro- and macrovascular complications increases in diabetic and hypertensive older individuals [33]. Patients should be actively and strongly discouraged from smoking. Nicotine replacement therapy in combination with pharmacotherapy should be offered to all individuals who are unable to quit smoking on their own [30].

A meta-analysis including 20 studies showed a 36% decline in mortality and a 32% decline in non-fatal myocardial infarctions after smoking cessation in patients with coronary artery disease [34].

The amount and type of alcohol has been standardized to two drinks or less per day. For men a maximum of 14 standard drinks every week and for women nine standard drinks every week are permitted [28]. A standard drink constitutes 142 ml or 5 oz of wine (12% alcohol), 340 ml or 12 oz of beer (5% alcohol), or 43 ml or 1.5 oz of spirit (40% alcohol) [4].

Evidence regarding the association of coffee and caffeine products with hypertension is conflicting and contradictory [35, 36]. An increased intake of coffee is associated with a steeper age-related increase in systolic blood pressure, especially in individuals over 70 years [37].

23.9 Pharmacological management

The choice of pharmacological agent, dosage, frequency, and timing of ingestion needs to be individualized to a patient's requirements. Although there is no clear consensus on the agent of first choice for use in a hypertensive and diabetic older person who does not have any other complications, yet it is widely held that either angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) should be used because of their ability to delay onset and progression of proteinuria in these patients. It is usual for a patient to need more than one agent to reach target blood pressures for adequate control. Calcium channel blockers (CCBs) or diuretics could be used in these situations. ACEIs and diuretics work well in combination and are advisable, while ACEIs in combination with ARBs have been shown to increase the risk of adverse cardiovascular events and should not be used. Adherence is usually better for ACEIs or ARBs but lowest for diuretics and beta-blockers. If one of the anti-hypertensive drugs is given at bedtime, it has been shown to reduce mortality in these patients. It is important to consider aspirin in hypertensive older diabetic patients for primary prevention.

ACEIs are the most studied group of drugs and have been advocated in several guidelines. ACEIs show beneficial effects in diabetic renal disease, myocardial infarction, and congestive heart failure [15]. They reduce the risk of stroke, coronary heart disease, and major cardiovascular diseases by 20–30% [38, 39]. Administration of ACEIs decreases the glomerular capillary pressure, with resultant reduction of glomerulosclerosis. ACEIs preserve GFR better in patients with subclinical proteinuria. ACEIs should be prescribed with caution in renal dysfunction and hyperkalemia, and are contraindicated in renal artery stenosis.

ARBs help in improving microalbuminuria and appear to be reno-protective [38, 39]. They delay the onset of microalbuminuria independent of their antihypertensive effect. ARBs may be useful alternatives in patients with heart failure who are unable to tolerate ACEIs. Angioedema, allergic reactions, and rash are rare side effects associated with their use.

Diuretics, especially thiazide diuretics, reduce major cardiovascular morbidity and mortality [15, 24, 40]. Low-dose chlorthathalidone has shown beneficial effects in reducing cerebro-vascular or cardiovascular accidents [24]. Thiazides also become important in patients with heart failure. They should be used in combination with ACEIs in patients with cerebrovascular disease. Dose-dependent adverse effects associated with their use include hypokalemia, hypomagnesemia, and hyperuricemia. They have synergistic effect with other antihypertensive agents such as ACEIs. However, potassium sparing diuretics should be avoided in combination with ACEIs.

CCBs have been promoted as agents of choice in many publications. However, they should be used cautiously in diabetic patients with cardiac morbidity such as congestive heart failure as they can camouflage pedaledema, which could be a side effect of CCB use [38, 39]. Combining CCBs (non-dihydropyridine) with ACEIs leads to greater reduction in proteinuria. Other groups of drugs should be cautiously used as per the requirement in special situations [38, 41].

β-blockers should be used with caution in older diabetic patients. Non-specific β-blockers are known to produce hypoglycemia unawareness and may result in frequent episodes of hypoglycemia [42, 43]. Cardioselective beta-blockers may be preferred when it is necessary to include these agents for uncontrolled hypertension. β-blockers may be used as first-line agents in patients who have features to suggest angina episodes. However, patients on β-blockers should be carefully monitored as they are known to disrupt metabolic control, especially in combination with thiazide diuretics.

A combination of β-blockers and the CCB Verapamil should also be avoided. α-adrenergic blockers should not be used as first-line therapy for hypertensive older diabetic patients.

23.10 Compliance with treatment and monitoring

Patients should be involved in their treatment and encouraged to monitor blood pressure in home surroundings using electronic (oscillometric) or manual mercury sphygmomanometers. Adherence to pharmacotherapy and lifestyle modification should be reassessed, reemphasized, and reinforced during every visit [4]. At least three readings of blood pressure should be taken during each visit. It is recommended that the first reading be discarded and average of the last two readings used to guide therapy.

23.11 Special situations of hypertension in diabetes

Areas of special attention when managing hypertension in a setting of diabetes include:

1. white-coat hypertension
2. isolated systolic hypertension
3. supine hypertension with orthostatic fall
4. ambulatory blood pressure measurement
5. home blood pressure measurement
6. frailty
7. advanced dementia
8. episodes of hypoglycemia
9. resistant hypertension
10. end of life situations.

23.11.1 White-coat hypertension

A difference in blood pressure recordings of more than 20/10 mmHg between clinic and average day-time ambulatory blood pressure is known as white-coat hypertension [12]. Due to an excessive sympathetic drive the patient has a spurious rise of blood pressure inside the clinic or office, often attributed to the anxiety experienced while interacting with a doctor in a white coat. To counter this effect, patients should be advised to follow home, ambulatory or out-of-office blood pressure monitoring.

23.11.2 Isolated systolic hypertension

As many as 15% older individuals have an elevated systolic blood pressure reading despite normal diastolic pressure [44]. This condition is called isolated systolic hypertension (ISH). Blood pressure should be reduced to a level lower than 160/90 mmHg using diuretics [12, 17, 45, 46]. Further lowering can be attempted if oral agents are tolerated well by the patient [47, 48]. Reduction of systolic blood pressure to lower than 160 mmHg decreases the incidence of stroke by one third and further lowering to below 150 mmHg imparts further benefit. Chlorthalidone reduces risk of non-fatal stroke, myocardial infarction, and left ventricular failure in patients with ISH [49, 50]. Potassium monitoring and supplementation is advocated when using chlorthalidone. Amlodepin has been found to be equally efficacious in this group [51–53].

Newer approaches have explored the use of aldosterone antagonists such as spironolactone and eplerenone as these agents reduce the arterial stiffness associated with ISH [54]. Nitrates have been found to act exclusively on systolic blood pressure but full effect usually takes at least 8 weeks of therapy.

23.11.3 Supine hypertension with orthostatic fall

Older diabetics are more likely to develop autonomic neuropathy. This leads to reactionary hypertension. Development of orthostatic hypotension should be carefully evaluated at every visit. It is diagnosed when there is a fall in blood pressure of more than 20/10 mmHg after standing from a supine position maintained for 1 min with resting tachycardia of more than 100 beats per minute [7, 55]. Thiazide diuretics are the most common offending agents. The patient should be well hydrated and a change of antihypertensive to CCBs should be considered [56].

23.11.4 Ambulatory blood pressure measurement

Blood pressure tends to be more labile in diabetic patients, necessitating repeated ambulatory monitoring over a longer periods [8]. This is also helpful in quantifying the usual nocturnal fall in diabetic patients, especially in the presence of autonomic dysfunction [19]. During ambulatory monitoring the blood pressure is measured twice every hour from 8:00 am till 10:00 pm (14 h) and a minimum of 14 readings are recorded [47].

For the diagnosis of hypertension, the average of the awake ambulatory systolic blood pressure recordings taken between 8.00 am and 10.00 am should be more than 135 mmHg or diastolic more than 85 mmHg, and the average blood pressure for 24 h should be more than 130 mmHg and diastolic more than 80 mmHg [4, 12]. This is helpful not only for diagnosing hypertension, but also evaluating white-coat hypertension drug resistance, hypotensive episodes, episodic hypertension, and autonomic dysfunction [12].

23.11.5 Home blood pressure measurement

Home blood pressure monitoring involves two recordings 1 min apart taken twice daily (morning and evening) with the person seated for at least 4 days in a week, ideally for 7 days [47]. Monitoring of blood pressure at home reduces white-coat hypertension [4, 57]. Patients should be educated to maintain a weekly chart as this improves control and drug compliance [57, 58].

23.11.6 Frailty

Frailty is a syndrome that is being increasing recognized in older individuals and signifies a state of decline in resistance to stressors due to decline in multiple physiological systems that lead to increase in adverse outcomes. According to some estimates as many as one in four older individuals can be classed as frail [59]. Diabetes itself is a pre-disability state and a risk factor for further development of frailty. It has been included as an important component in most frailty indices used today. Reduced muscle mass and sacropenia have been associated with reduced insulin sensitivity and decreased glucose uptake, and hence increase the risk of insulin-resistance syndrome in older people with diabetes [31, 32]. The blood pressure control target among frail older diabetics should be below 150/90 mmHg [7, 60]. Amino acid supplementation has been reported to improve insulin sensitivity and lean body mass in these subjects [31, 32].

23.11.7 Advanced dementia

Diabetic and hypertensive older persons are at an increased risk of developing dementia. Those individuals with advanced dementia who are also diabetic and hypertensive may have a significant limitation of functionality and independence. A slight relaxation in the blood pressure targets to be achieved in these patients should be worked out depending on individual patient requirements. Blood pressure control should be limited unless this is immediately life-threatening.

23.11.8 Episodes of hypoglycemia

Frequent hypoglycemia episodes could lead to hypoglycemic brain damage and other co-morbidities, unmasking and destabilizing previously independent and functional older diabetic individuals. The morbidity and impact of such episodes can be critical for individual patients and families, and it is important to closely monitor and be alert for these episodes. Polypharmacy, errors in insulin administration, incorrect prescriptions, erratic meals, renal impairment and liver dysfunction, and cognitive impairment could all contribute to the development of hypoglycemic episodes. The role of beta-blockers in producing hypoglycemia unawareness and resultant deterioration in health has already been emphasized.

23.11.9 Resistant hypertension

Resistant hypertension is defined as a persistent blood pressure recording above the optimal range despite lifestyle modifications and maximal tolerable antihypertensive therapy, including diuretics. It is more commonly seen in older individuals owing to increased arterial stiffness, decreased antihypertensive efficacy, and higher incidence of organ damage [40]. Before a diagnosis of resistant hypertension is made, pseudo-resistant hypertension should be ruled out. This includes lack of blood pressure control due to poor drug compliance, which may be secondary to polypharmacy, frailty, dementia, and white-coat hypertension [48]. Obstructive sleep apnea syndrome and other medical causes associated with chronic conditions like renal impairment, atherosclerotic heart disease, and peripheral vascular disease may contribute to worsen the situation. Other causes of secondary hypertension (pheochromocytoma, primary aldosteronism, renal artery stenosis, and Cushing`s syndrome) are the usual culprits, but are often overlooked [40, 48].

23.11.10 End-of-life situations

Patients receiving end-of-life care are most often ignored in contemporary guidelines on control and monitoring of blood pressure. It is commonly held that in these situations using antihypertensive agents to control blood pressure only increases the pill burden and reduces the

quality of life without altering the morbidity or mortality profile. The IDF recommends that unless blood pressure is immediately life-threatening, control should not be attempted in such situations.

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CHAPTER 24
Hypoglycemia

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KEY MESSAGES

- Hypoglycemia can be a frightening experience in older adults and may lead to a fear of the condition, with a negative impact on quality of life and mood.
- The risk of hypoglycemia is a major consideration, as the consequences of hypoglycemia are immediate and lead to clinical, functional, and psychological morbidity with a significant negative impact on overall quality of life.
- A catastrophic outcome of hypoglycemia in older adults is the high risk of falls.
- With aging comes a lower intensity and more limited perception of autonomic symptoms during hypoglycemia compared with the younger population.
- Marked subjective unawareness of hypoglycemia in the older cohort can sometimes be present.
- The risk of hypoglycemia may be higher in lower education and income groups, and in the presence of renal impairment, microalbuminuria (even with normal renal function), and polypharmacy, especially certain classes of medications such as ACE inhibitors and non-selective β-blockers.
- Sulfonylurea and insulin therapy are associated with higher risks of hypoglycemia than other glucose-lowering medications.
- The benefits of tight glycemic control are not clear and should be carefully weighed against the risk of hypoglycemia in the older population.
- A simplified insulin regimen in older adults can lower the risk of hypoglycemia, while maintaining glycemic control.

24.1 Introduction

Over the past two decades there has been a focus on tighter glycemic control in the general population to decrease the risk of diabetes-related complications. Management of diabetes and the importance of preventing complications by adequate glycemic control are as important in the older population as in younger adults. However, in older adults, the risk of hypoglycemia is a major consideration, as the consequences of hypoglycemia are immediate and lead to clinical, functional, and psychological morbidity, with a significant negative impact on overall quality of life. Clinicians constantly need to balance the benefits of reducing hyperglycemia against the risk of hypoglycemia. However, recently it has become clear that enthusiasm in improving glycemic control has resulted in higher risk of hypoglycemia, particularly in the older population. The results of a retrospective observational study of the national trends in US hospital admissions using data from over 33 million Medicare beneficiaries >65 years between 1999 and 2011 [1] show that the admission rate for hyperglycemia decreased by 55.2% during this time period while the rate for hypoglycemia decrease by 9.5%. Thus, the admission rate for hypoglycemia now exceeds that for hyperglycemia [1]. Most of the published guidelines for managing diabetes in older adults suggest liberating glycemic goals to decrease the risk of hypoglycemia [2–4]. However, there is still a need for more education amongst clinicians. The knowledge

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gap is apparent in a retrospective cohort study evaluating US national veteran affairs hospitals from 2008 to 2009. The results showed that 52% of the patients in the study had tight glycemic control as defined by HbA1c < 7%. The patients with tight control were older, had more co-morbidities, including dementia, had recent weight loss, and the majority were taking either insulin or sulfonylurea, putting them at higher risk of hypoglycemia [5]. The high financial and personal cost of hypoglycemia in older adults has resulted in serious public health problems world-wide, and indicates the need for better management strategies to improve hyperglycemia without increasing the risks of hypoglycemia.

24.2 Epidemiology and risks of hypoglycemia

Hypoglycemia prevalence is difficult to measure due to variable definitions of hypoglycemia in the literature and surveillance systems. Traditionally, hypoglycemia was documented by Whipple's triad, which includes a low measured plasma glucose concentration, symptoms and/or signs of hypoglycemia, and resolution of these symptoms/signs after the glucose concentration is raised. However, with technological advances, recognition of hypoglycemia has changed in recent decades. In the majority of studies hypoglycemia prevalence is still measured by patient report which, in the case of mild to moderate episodes, remains highly unreliable. These numbers are variable and usually underestimate the prevalence of hypoglycemia due to the hypoglycemic unawareness commonly found in older patients with diabetes. Some studies report only severe hypoglycemia requiring third-party assistance. This method also misses unrecognized or unreported episodes. In addition to hypoglycemic awareness, nocturnal hypoglycemia leads to further difficulty in appropriate recognition and treatment of hypoglycemia. A study evaluating capillary blood glucose results recorded during acute hospitalization showed that the greatest risk of hypoglycemia in these patients was overnight, with peak occurrence between 3am and 4 am [6]. In patients with type 1 diabetes, approximately 50% of severe hypoglycemic episodes occur at night [7]. As glucose monitoring is rarely performed during the night, and as symptoms are not felt during the sleep, most of these episodes remain unaccounted for in the studies.

In general, hypoglycemia is more common in patients with type 1 diabetes compared to type 2 diabetes. Treatment modalities impact the risk of hypoglycemia in patients with type 2 diabetes, being highest in those treated with insulin and sulfonylurea. However, type 1 patients still have a higher risk compared to insulin-treated patients with type 2 diabetes. In a population-based study, the incidence of hypoglycemia in patients with type 1 diabetes was three times more than in patients with insulin-treated type 2 diabetes [8]. In both types of diabetes patients with longer duration of disease have higher frequency of hypoglycemia. In a study performed by the UK Hypoglycemia Study Group the incidence of severe hypoglycemia was 110 episodes per 100 patient years in patients treated with insulin for <5 years compared to 320 episodes per 100 patient years in those with >15 years of treatment [9]. In the same study, for patients with type 2 diabetes, those treated with insulin for <2 years had 7% incidence of hypoglycemia compared to 25% in those treated for >5 years.

24.3 Altered physiological response to hypoglycemia with aging

The counter-regulatory hormonal system is an important defense mechanism against hypoglycemia in all people with and without diabetes. When glucose levels in the body decrease, there is a decrease in insulin secretion, combined with an increase in glucagon secretion. Aging is associated with progressive changes in carbohydrate metabolism. These changes are responsible for higher risks of both diabetes and hypoglycemia in the older population. The major hormones responsible for glucose counter-regulation include glucagon for acute hypoglycemia, and growth hormone and cortisol for prolonged hypoglycemia. In the aging population there is an altered release of these counter-regulatory hormones. Meneilly *et al.* showed reduced secretion of glucagon and growth hormones in older patients with diabetes compared to younger adults [10]. Other studies have also shown age-related impairment in epinephrine and glucagon secretions, which increases the risk of hypoglycemia due to deficient counter-regulation [11].

24.4 Hypoglycemic unawareness

Symptoms of hypoglycemia are critical in the recognition and treatment of hypoglycemic episodes by patients. These symptoms are triggered by the activation of the sympathetic and parasympathetic autonomic nervous systems, which are activated via secretion of the counter-regulatory hormones. In individuals without diabetes, the counter-regulatory hormone secretion occurs when blood glucose levels fall below the normal range (approximately <3.8 mm) [12, 13]. The symptomatic response to hypoglycemia occurs around 3.0 mM and the onset of neuroglycoenic symptoms and cognitive dysfunction occurs around 2.8 mM [13] (Figure 24.1). Thus, normally the secretions of the counter-regulatory hormones begin at a higher glucose level than that needed for symptomatic response, preventing hypoglycemic episodes. With aging, there also seems to be a lower intensity and more limited perception of autonomic symptoms compared to the younger population [10]. The impact on perception with aging is seen in patients with both type 1 and type 2 diabetes, leading to a reduction in or absence of symptoms when hypoglycemic thresholds are reached [10, 14]. In a study evaluating counter-regulatory responses with aging, when hypoglycemia was induced by insulin infusion in non-diabetic older adults, the counter-regulatory response, in the form of

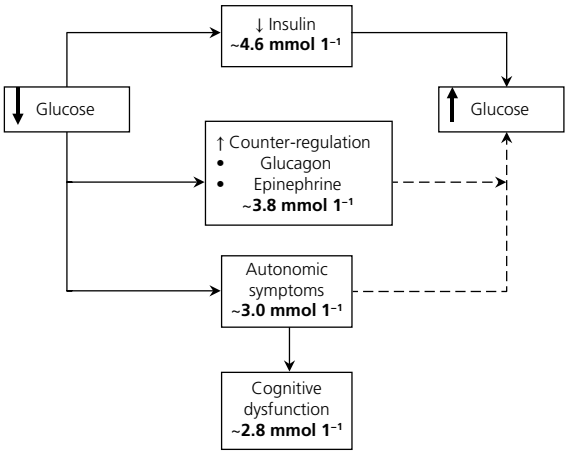

Figure 24.1 Hierarchy of responses to hypoglycaemia in non-diabetic humans.

secretion of growth hormone and cortisol, was lower than in younger adults [11]. There was also an attenuation of blood glucose recovery in these older individuals, with lower insulin clearance and secretion of glucagon. Another study testing hormonal, subjective, and cognitive responses to hypoglycemia in older and middle-aged patients with type 2 diabetes showed marked subjective unawareness of hypoglycemia in the older cohort [15].

In addition to alteration in the counter-regulatory response, there is also altered clinical presentation with aging. A study evaluating the symptoms of hypoglycemia in different age groups showed that healthy non-diabetic older adults showed an absence of tachycardic response and lower symptom score, despite similar counter-regulatory hormone response during a hyperinsulinemic glucose clamp [16]. Such results suggest an impaired response to autonomic stimulation in older adults, leading to delayed or absent adrenergic warning symptoms that are typical of a hypoglycemic state in a younger population. Thus, there is a difference in which symptoms present first. As the symptomatic response to hypoglycemia starts at a lower blood glucose concentration in older adults compared to the younger population [17], the glucose level triggering the adrenergic symptoms starts closer to the level at which neurological symptoms occur. Studies evaluating neuroglycopenic symptoms have shown more severe cognitive impairment and lack of prior warning symptoms during hypoglycemic periods in older men compared to younger men without diabetes [17]. This phenomenon has been shown in several studies, indicating a difficulty in the perception of symptoms traditionally contributing to hypoglycemia.

Another aspect of hypoglycemia in the elderly population is the variable presentation of symptoms. A study of elderly patients on insulin or sulfonylurea showed that symptoms of hypoglycemia were non-specific and included weakness, dizziness, sleepiness, and unsteadiness [18]. The presence of prominently neuroglycopenic symptoms may be misconstrued as other common co-morbidities such as orthostatic hypotension, transient ischemic attacks, vertigo, or syncope, and may remain undiagnosed. In addition to the concern about unawareness, there have been some

Table 24.1 Common hypoglycemia symptoms in older adults.

Neuroglycopenic	Autonomic	Neurological
Weakness	Sweating	Unsteadiness
Dizziness	Shaking	Poor coordination
Confusion	Palpitation	Visual disturbances
Lightheadedness	Anxiety/panic	Speech difficulty
Inattention		

suggestions that older patients who do not have impaired awareness may have a higher cut-off level at which they feel hypoglycemic symptoms. In a study assessing symptoms of hypoglycemia in older adults, those who reported being aware of the hypoglycemia symptoms felt them at a higher cut-off level compared to the generally accepted level of <4 mmol/l [19].

Other factors influencing hypoglycemic awareness in the aging population include medications such as β-blockers, hypnotics, and tranquilizers, alcohol use, neuropathies, diseases that interfere with cerebral blood flow, and cognitive dysfunction interfering with recognition of symptoms. Thus, a combination of factors leads to increased risk, decreased or delayed identification, and inadequate treatment of hypoglycemia in the older population. It is therefore important for clinicians to remain vigilant about the possibility of hypoglycemic unawareness and the presence of atypical/altered presentation of hypoglycemia in order to avoid recurring hypoglycemia and its poor consequences. Table 24.1 lists common symptoms of hypoglycemia in the older population.

24.5 Risk factors for hypoglycemia in aging

Increasing age is a risk factor for hypoglycemia. A retrospective observational analysis of Medicare population in the USA showed that between 1999 and 2011, the rate of severe hypoglycemia requiring hospitalization was two-fold higher in patients >75 years of age compared to 65–74 years of age [1]. Another population-based study looking at the incidence and risk factors for severe hypoglycemia in a population over 65 years of age found advanced age to be an independent risk factor for severe hypoglycemia [20]. Severe hypoglycemia is commonly seen in the older population and is found to be more common when associated with co-morbid conditions and aggressive therapy with insulin or sulfonylurea [21].

Risk of hypoglycemia seems to increase with longer duration of diabetes. In a study conducted in South Korea, over 1000 patients were followed for a median of 10.4 years. The results showed that the risk of severe hypoglycemia was independently associated with duration of diabetes [22]. Another observational study conducted in six UK secondary-care diabetes centers over 9–12 months followed >350 patients. The results of this study showed that in the early disease period (<2 years duration of diabetes), insulin-treated patients with type 2 diabetes had low rates of hypoglycemia. However, the patients taking insulin for >5 years had much higher prevalence of mild and severe hypoglycemia, comparable to patients with type 1 diabetes of short duration [9].

Socioeconomic status and education also have an impact on the risk of hypoglycemia. A cross-sectional analysis assessed the risk of hypoglycemia in a population of over 14,000 multilanguage, ethnically-stratified persons with a mean age of 58 years. The risk of hypoglycemia was higher in the lower income (<$24,000/year) group vs the higher income (>$65,000/year) group (16% vs 8.8%), and those with lower education (<high school diploma) compared to the group with higher education (>college degree) (11.9% vs 8.9%) [23]. Other factors associated with higher risk of hypoglycemia include renal impairment [21], microalbuminuria even with normal renal function [22], polypharmacy, and certain classes of medications such as ACE inhibitors and non-selective β-blockers [24]. In addition, ups and downs in overall health, infections, hospitalizations, or even social stresses that lead to dietary changes and weight loss may increase the risk of hypoglycemia.

A bidirectional relationship is noted between cognitive dysfunction and hypoglycemia. Cognitive dysfunction may result in difficulty in identification of hypoglycemic symptoms, delayed treatment of hypoglycemia, and a delay in reporting the episodes to the medical provider. When any of these steps are missed, the hypoglycemia remains unrecognized by clinicians, leading to the

continuation of the regimen that caused the hypoglycemia. Several large studies have shown a higher risk of hypoglycemia in patients with coexisting cognitive dysfunction. A prospective cohort analysis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study evaluated the effect of baseline cognitive function and cognitive decline over a 20-month follow-up period on the risk of severe hypoglycemia [25]. The results showed that in patients with poor cognitive function at baseline there was an increased risk of severe hypoglycemia. In addition, those patients who had cognitive decline over the next 20 months had a higher risk of subsequent hypoglycemia when their baseline cognitive function was poor. Another retrospective cohort study of national veterans' affairs in the USA found that older veterans with diabetes and dementia were at high risk of hypoglycemia, especially when they were on an intensive diabetes treatment regimen [5].

There is a similar bidirectional relationship recognized between hypoglycemia and frailty [26]. Although the definition of frailty is not well standardized, it is usually characterized by a decline in physiological reserve and a difficulty overcoming physical and psychosocial stressors. The impact of frailty is frequently mediated through under-nutrition, which is common in frail older patients and should be carefully evaluated.

24.6 Clinical implications of hypoglycemia

Aging and diabetes are associated with higher prevalence of coexisting medical conditions. Various co-morbidities can impact the risk of hypoglycemia in older adults. On the other hand, hypoglycemia also increases the risk of other medical conditions. Both short-term and long-term complications of hypoglycemia are common in the older population.

24.6.1 Short-term implications

Hypoglycemia can be a frightening experience in older adults and may lead to a fear of hypoglycemia, with a negative impact on quality of life and mood [27]. In addition, fear of hypoglycemia results in overtreatment of low glucose levels, leading to high glucose variability and emotional stress and anxiety [28].

Hypoglycemia during hospitalization is quite common. Episodes of hypoglycemia in a hospital setting have led to adverse outcomes in older patients. A retrospective study in older adults evaluated the association between number and severity of hypoglycemia (<50 mg/dl) and inpatient mortality, length of stay, and mortality 1 year after discharge [29]. The results showed that each additional day with hypoglycemia during the hospitalization was associated with an increase of 85.3% in the odds of inpatient death and 65.8% in the odds of death within 1 year of discharge. The patients with hypoglycemia during hospitalization had longer hospital stay. The length of stay increased by an average of 2.5 days for each day with inpatient hypoglycemia.

Another catastrophic outcome of hypoglycemia in older adults is the high risk of falls. Older adults with diabetes and a history of hypoglycemia have a high risk of falls and fall-related fractures, which are particularly worrisome outcomes of hypoglycemia due to its impact on quality of life. A retrospective observational study of patients >65 years of age showed that outpatient hypoglycemic events were independently associated with an increased risk of fall-related fractures. The patients with type 2 diabetes who had any history of hypoglycemic event had 70% higher odds of fall-related fractures compared to those who never had a hypoglycemic event (5.24% vs 2.67%) [30].

24.6.2 Long-term implications

Recurrent hypoglycemia also increases the risk of long-term complications. Large epidemiological studies have shown that both hyperglycemia and hypoglycemia lead to increased risk of cardiovascular complications. In a retrospective cohort study in the UK, hypoglycemia was associated with increased risk of cardiovascular events and all-cause mortality in patients with type 1 or insulin-treated type 2 diabetes [31]. The median time from the first hypoglycemic event to the first cardiovascular event was 1.5 years, indicating a long-lasting impact of hypoglycemia. Another large prospective study comparing intensive versus standard glycemic control showed that severe hypoglycemia was associated with higher risk of major macrovascular events

(HR 2.88), microvascular events (HR 1.81), death from cardiovascular causes (HR 2.68), and death from any cause (HR 2.69) [32]. Even self-reported hypoglycemia has been shown to be associated with a 3.4-fold higher risk of mortality over a 5-year period in a large retrospective study [33].

Higher risk of dementia is another important consequence of recurrent hypoglycemia over a period of time. Brain function is highly dependent on blood glucose levels as a source of energy and in older adults it is particular vulnerable to low glucose levels. A population-based prospective study of older adults reported that during the 12-year follow-up period, patients experiencing hypoglycemia had a two-fold higher risk of developing dementia compared to those without hypoglycemic episodes [34]. This study also showed that patients with a diagnosis of diabetes who developed dementia had a greater risk of experiencing subsequent hypoglycemia compared to those who did not develop dementia. Thus, the relationship between dementia and hypoglycemia is thought to be bidirectional. Another longitudinal cohort study from 1980 to 2007 found that older adults with one or more episodes of severe hypoglycemia had more than a two-fold risk of developing dementia compared to those without hypoglycemia [35]. It is important to treat older patients with diabetes and cognitive function carefully, as treatment modality impacts their risk of hypoglycemia. Older patients with cognitive dysfunction may not be able to cope with complex insulin therapy, leading to treatment errors and higher risk of hypoglycemia. Most experts suggest liberalizing glycemic control in people with diabetes and dementia, but recent studies have shown that such individualized approaches are not always common. A study in older veterans in the USA examining the relationship between diabetes and cognitive dysfunction showed that diabetes was managed more intensively in those with cognitive impairment. A patient-centered approach to establishing glycaemia goals and choosing treatment modality is important to improve the management of diabetes in older adults.

One of the most important areas to consider in older adults with chronic disease is the impact on quality of life. An observational study in the USA evaluating a race-stratified random sample of over 6000 older adults with type 1 or type 2 diabetes found that hypoglycemia was associated with lower health-related quality of life (HRQL) [36]. The degree of impact of hypoglycemia on HRQL was comparable to that caused by diabetes complications. This is an important issue that must be considered when management strategies and glycemic goals are decided in older adults.

24.7 Glycemic control and hypoglycemia in aging

Landmark studies in the 1990s showed that improving glycemic control improved the risk of long-term complications in both type 1 and type 2 diabetes [37, 38]. The results of these studies have led to better management of diabetes and a push towards tighter glycemic control for prevention of complications. This approach has also led to a higher prevalence of hypoglycemia, especially in patients treated with insulin. A large observational survey of over 9000 participants in the USA reported that severe hypoglycemia requiring third-party assistance was more frequent in patients with extremes of glycemic control, that is, HbA1c <42 mmol/mol (<6%) or >75 mmol/mol (>9%) [39]. More recently, studies have tried to evaluate the relationship between hypoglycemia, tight glycemic control, and poor health outcomes, including mortality. A retrospective study from the UK assessed survival as a function of HbA1c. This study evaluated data on patients >50 years of age with type 2 diabetes from the UK General Practice Research Center Database from 1986 to 2008 [40]. They found a U-shaped relationship between survival and HbA1c, with low and high mean HbA1c values associated with increased all-cause mortality and cardiac events. The higher mortality with lower HbA1c value in this study is thought to reflect the risk and impact of hypoglycemia. A recent analysis of the hypoglycemia and clinical outcome data from another large study evaluating the impact of intensive versus standard glucose lowering on primarily cardiovascular outcomes showed that the rates of severe hypoglycemia in the group assigned to the intensive control were much higher than those with standard control (2.7% vs 1.5%) [32]. Other smaller studies have also shown a higher risk of

unrecognized hypoglycemia with tighter glycemic control. In a small study using continuous glucose monitoring (CGM) to assess patients with type 2 diabetes, unrecognized hypoglycemia occurred more frequently and lasted longer in patients with HbA1c < 7% (Engler 2011).

Many guidelines and consensus papers focusing on the management of diabetes in older adults recommend avoiding tight glycemic control [3, 4]. The guidelines recommend individualizing HbA1c goals based on patients' co-morbidities, functionality, and cognitive status. However, a recent cross-sectional analysis of data on over 1200 adults >65 years of age with diabetes from the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2010 showed that the HbA1c level was the same whether patients were healthy or had significant co-morbidities [41]. In another cross-sectional analysis of veterans >65 years of age, diabetes was managed more intensively in older veterans with dementia and cognitive impairment, with 30% on insulin compared to 24% who were not on insulin therapy. Hypoglycemia was more frequently seen in insulin-treated patients when they had dementia (26.5%) compared to patients without cognitive dysfunction (14.4%) [42]. Thus, more work needs to be done in educating clinicians regarding the risks and benefits of tight glycemic control.

24.8 HbA1c and hypoglycemia in aging

HbA1c is used as the gold standard test to assess long-term glycemic control in the management of diabetes, and is now also recommended for use in the diagnosis of diabetes. HbA1c reflects average mean glucose over the past 90 days, which is typically the life span of a red blood cell (RBC). In an aging population, multiple conditions affect RBC life span and thus measurement of HbA1c. These conditions include various types of anemia, bleeding and transfusions, renal insufficiency, uremia and acidosis, and erythropoietin deficiency. Thus, it is important to avoid the use of HbA1c as a sole measure of glycemic control to make treatment changes. Treatment decisions solely based on HbA1c may lead to hypoglycemia if the HbA1c value is erroneously high due to other conditions. The measurement of HbA1c also misses glucose variability and excursions that occur on a day-to-day basis. A small study assessed the risk of hypoglycemia by CGM in 40 patients >70 years of age with HbA1c >8% [43]. The results showed that one or more episode of hypoglycemia as defined by CGM < 70 over a 3-day period occurred in 65% of the older patients. Out of all patients with hypoglycemia, 54% had an HbA1c between 8% and 9%, while 46% had HbA1c > 9%. Out of a total of 102 hypoglycemic episodes occurring during the study, 46% of the episodes had glucose < 50 mg/dl. Thus, it is important to keep in mind that simply liberating HbA1c goals may not be sufficient to resolve the risk of hypoglycemia in older adults.

24.9 Role of treatment modalities

The treatment modality in the management of diabetes confers different risks of hypoglycemia. Recent times have seen the invention of many new classes of glucose-lowering agents. With the availability of multiple classes of new agents, there is more flexibility in targeting hyperglycemia at different times of the day and avoiding the risk of hypoglycemia. However, the cost of the newer classes of medication prevents their widespread use world-wide.

Sulfonylurea and insulin remain two of the most commonly used glucose-lowering agents. Different agents in these classes confer different risks of hypoglycemia. A study comparing long- versus short-acting sulfonylurea in patients with type 2 diabetes concluded that severe hypoglycemia leading to hospital admission is more common in elderly patients treated with long-acting compared to short-acting sulfonyl urea [44]. A retrospective nationwide study from Denmark evaluating outcomes in patients treated with sufonylurea or metformin in combination with insulin showed that when combined with insulin, sufonylurea was associated with a higher risk of hypoglycemia, as well as mortality, compared to metformin [45].

Insulin is an important agent in the management of diabetes in all age groups. However, it has a significant impact on the risk of hypoglycemia. In recent years, insulin has been increasingly used earlier in the treatment of type 2 diabetes. During the last decade, the number of patients in the USA with insulin-treated diabetes rose by 50%. A nationally representative public health survey of adverse drug events among

insulin-treated patients showed that insulin-related adverse drug events required more than 97,000 emergency department visits annually, out of which one-third resulted in hospitalization [46]. Over 60% of these patients seeking emergency care suffered from severe neurological sequelae. Amongst the study cohort, insulin-treated patients >80 years of age were more than twice as likely to visit the emergency department and five times more likely to be subsequently hospitalized than those between 45 and 64 years old age. This risk was highest in patients taking only insulin, compared to insulin combined with other non-insulin agents. Another retrospective cohort study assessed a nationally representative population in the UK for an association between hypoglycemia, risk of cardiovascular events, and all-cause mortality [31]. The results showed that in insulin-treated patients with either type 1 or type 2 diabetes, and those with or without history of pre-existing cardiovascular disease, hypoglycemia was associated with an increased risk of cardiovascular events and all-cause mortality.

The complexity of diabetes management is important for both success in achieving optimal glycemic control and avoiding the risk of hypoglycemia. Treatment complexity may be more than an older patient's ability to cope with the regimen, and as a consequence the management strategy tends to fail and the risk of glucose excursions, including hypoglycemia, increases. A cross-sectional data-based analysis of veterans >65 years of age with diabetes showed that the risk of hypoglycemia was much higher when patients with cognitive dysfunction were give treatment regimens with higher complexity [42]. There are not many studies evaluating the impact of de-intensification of the regimen. A small retrospective study evaluated the impact of simplification of the regimen in insulin-treated patients by decreasing the number of insulin injections [47]. The results of this study showed that simplifying the regimen improved glycemic control, while decreasing the number of reported hypoglycemic episodes. A recent prospective study simplified insulin regimens in older adults (>70 years of age) on multiple insulin injections per day who had hypoglycemia (glucose < 70 mg/dl) on CGM [48]. The simplification involved the use of once-a-day basal insulin, combined with non-insulin agents, to lower post-meal glucose levels. The results of this study show that the duration of hypoglycemia decreases on simplified regimens, without a change in glycemic control. Simpler regimens also decreased the disease-related distress in older patients.

24.10 Conclusions

Hypoglycemia in older adults is common and has poor consequences. Symptoms of hypoglycemia may be different or absent in older adults. The benefits of tight glycemic control are not clear and should be carefully weighed against the risk of hypoglycemia in this population. Treatment modalities with lower risk of hypoglycemia should be preferred if affordable. Target-based management strategy using HbA1c as the sole indicator may result in more harm than good. Liberating HbA1c goals alone may not decrease the risk of hypoglycemia in older adults. A simplified regimen that matches patients' ability to perform self-care is important in lowering the risk of hypoglycemia.

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CHAPTER 25
Diabetes in care homes

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KEY MESSAGES

- Diabetes and its complications are important reasons for admission to a care home.
- Older people with diabetes in care homes are highly vulnerable and require complex nursing and medical care in addition to assistance with personal hygiene.
- The quality of diabetes care within care homes and staff knowledge and competence to care for older people with diabetes who require complex care must improve. Implementing evidence-based guidelines and enforcing relevant policies and regulations is required to improve the current situation in many countries.
- Screening for diabetes at the time of admission to a care home and regularly afterwards is important.
- Hypoglycemia is the most common side effect of insulin and sulfonylureas.
- Risk factors for hypoglycemia are highly prevalent in care homes.
- Maintaining health status and functional capacity, and eventually a dignified end of life using individualized care plans are key care goals for all residents with diabetes.

25.1 Introduction

There is a great deal of discussion about the fact that baby boomers, people born between 1946 and 1964, are turning 65 and many have diabetes, which contributes to the global prevalence of diabetes in older people and the resultant pressure on health services. It also heralds a need to consider the unique needs of older people with diabetes, many of whom will require nursing home care. It is projected that the number of people aged over 65 years will increase between 2000 and 2050 from 9.3 million to 17 million. In addition, a four-fold increase is anticipated in the number of people over age 8 years, from 1.1 million to 4.4 million [1]. Independent living may be increasingly difficult for many older people who develop chronic illness, including diabetes, become frail and may become increasingly isolated. Diabetes is an independent risk factor for admission to a care home [2] and is implicated in up to a quarter of admissions [3].

In the industrialized nations, increasing numbers of older people continue to move into aged-care homes where their physical and social needs may be better met. In the USA, apart from chronic care settings such as nursing homes, there is a growing industry of assisted-living facilities that provide services such as meals, supervision, leisure, and cleaning. In other countries, such as Australia, low-level hostels and "home care" packages provide similar care and services for many older people and support them to remain self-caring and relatively independent. The organization, staffing, and operation of such services/facilities affect the nature of the health and social care provided to residents and impact on the quality of care delivered, irrespective of the person's health condition.

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Older people receiving home care, including after discharge from hospital, are vulnerable and often have unmet needs [4]. Some care staff have little training beyond assisting with activities of daily living (ADL), yet older people require complex assessment, care, monitoring, and treatment, and have complicated medicine regimens that include high-risk medicines such as insulin and anticoagulants.

25.2 The UK as a model of care home reform

In the UK, after World War 2, the 1948 National Assistance Act established the local authority as the responsible body for overseeing the reform of public assistance institutions, which originated from the Elizabethan Poor Law, and the creation of residential care homes for older people "in need of care and attention".

Improvements to bed availability were slow and hampered by a lack of funds. Residents were frail and increasingly dependent, but fewer hospital beds for frail older people were being provided, which put pressure on local authorities and social services to support the care of frail older people at home and in residential and nursing homes. During the 1980s there was an expansion of the independent sector to complement (or compete with) social services provision. Between 1982 and 1991, the number of beds in private care homes rose from 49,900 to 161,200 [5]. However, the free provision of care within these homes depend on residents having a low level of wealth. As increasing numbers of frail older people move into private care homes, National Health Service (NHS) long-stay hospital beds have closed, so that more than 50% of all healthcare beds in the UK are now provided in nursing homes [6].

As a result of these trends, more people are living in care homes and UK estimates are that the current care home population of 450,000 will increase to 1,130,000 in the next 50 years, and will be associated with escalating social and health costs of providing care from £13 billion to £55 billion by the year 2051 [7]. In the UK, Section 49 of the Health and Social Services Act 2001 made care provided by registered nurses in care homes an NHS responsibility, and thus free of charge. Hence, the nomenclature is intimately linked with the costs of care and eligibility for free care funded by the UK healthcare system (NHS).

Since 2004, the Commission for Social Care Inspection (CSCI) has incorporated the roles of the Social Services Inspectorate (SSI), the joint review team of the SSI, the National Care Standards Commission (NCSC) and the Audit Commission in the UK. Further reorganization of regulatory services is anticipated, incorporating the Healthcare Commission and the Mental Health Act commission. The CSCI and its successor will have responsibility for the regulation, inspection, and review of social care services. In particular, they will inspect care homes and rate them, according to national standards, as well as reviewing local councils' provision of advice and purchase of services. According to the UK Commission for Social Care Inspection, the distinction between *residential* and *nursing* homes is that:

- *residential care homes* provide either short- or long-term accommodation, meals, and personal care (such as help with washing and eating, sometimes termed *personal care only*)
- *nursing care homes* offer the same as residential care homes but they also have *registered nurses* who can provide care for more complex health needs.

The distinction between residential and nursing care applies to individuals. Although residents may enter a home requiring only assistance with personal care, they are likely to become increasingly frail and eventually require a nursing bed. While this may necessitate a move, many homes offer both residential and nursing care, allowing the resident to remain in the same home. Other aspects of specialist care include residents with mental health disorders, who often require both residential and nursing care. Finally, there is an increasing population of older adults with learning disabilities who are no longer cared for in psychiatric hospitals [8].

Some countries have "aging in place" programs that prevent or delay admission to an aged-care home [4], but some residents require medical and nursing care not just help with ADLs and are at risk of admission to hospital.

25.3 Epidemiology

A number of studies and surveys of diabetes prevalence have been performed, and the key references for these are presented in Table 25.1. In the USA the proportion of residents with diagnosed diabetes increased from 14.5% to 24.6% between 1979 and 2004 [9]. This may represent an increase in the prevalence of type 2

Table 25.1 Some estimates of diabetes prevalence among older care home residents.

Source country	No. of patients/ residents	Criteria	Prevalence (%)	Comments
Wisconsin, USA, 1979 [10]	7850 (approx.)	Self-reported	10	A community-based study: 0.9% of cases living in nursing homes 17.5% of adults aged 80+ years were in nursing homes
Toronto, Canada, 1965–86 [11]	1177	Newly diagnosed	30–35	Longitudinal study of care home residents not diabetic at admission on OGTT
US National Nursing Home survey, USA, 1979		Self-report	14.5	Difficulty in collating data from this report
Wales, UK, 1997 [12]	1514	Self-report	7.2	Study was not aimed at screening new cases but at looking at characteristics of known cases
Liverpool, UK, 1997 [13]	1611	Self-report	9.9	Primarily a description of the quality of care
Germany, 2001 [14]	1936	Self-report	26.2	Study also examined the undiagnosed population, but used HbA1c as diagnostic test Data not considered here
Birmingham, UK [3]	636	Self-report Plus OGTT	12.0 26.7	The first study to use a screening test WHO 1998 criteria used Details given of those unable to participate
USA, 2004 [9]	549,125	Self-report	26.4	This review of all new admissions to care homes during 2002 suggests that diagnostic coverage has improved
Newcastle, UK, 2006 [15]	1461	Self-report plus fasting/ postprandial glucose	11.4 19.9 19.9	Fasting and postprandial glucose used to increase coverage but may have resulted in underestimate of prevalence Difference in prevalence between residential, nursing, and EMI care homes found
New Zealand, 2006 [16]	1567	Self-report	11.7	
Norway, 2006 [17]	788 186	Self-report HbA1c/OGTT	20.2 0.5 0.5	Including frail older people in their own homes but the majority (427) were unfit to participate Patients had to have a raised HbA1c in order to be eligible for OGTT screening
Geelong, Australia, 2013 [18]	270	Chart audit using the AUSDRISK tool		36% had more than four risk factors and 68% had symptoms suggestive of diabetes Indicative only

OGTT, oral glucose tolerance test; EMI, elderly mentally infirm.

diabetes in the USA and possibly increased survival, but increased screening and diagnosis of diabetes may explain some of this trend. European estimates of self-reported diabetes are much lower, but when studies are augmented by the direct assessment of glucose tolerance, the estimated prevalence exceeds 20%. Such studies thus identify a large population who are unaware of their abnormal glucose tolerance.

Importantly, the prevalence of type 1 diabetes is increasing and people with type 1 diabetes are surviving into older age and have specific and different care needs from older people with type 2 diabetes. Thus, establishing the type of diabetes is essential to planning appropriate care, especially medicines and monitoring regimens.

These data highlight important challenges, including the fact that widespread screening programs might not be practical or warranted, and glucose tolerance tests are often not practical and fasting glucose may miss cases of diabetes. Likewise, postprandial testing may be more useful but will also miss cases. HbA1c is increasingly used to diagnose diabetes and can be used to consider cardiovascular as well as diabetes risk and treatment options.

25.4 Complications and co-morbidity

Chronic disease is common among care home residents, compared with older people living in the community, but the quality of care for older people living in care homes may be worse than for those living at home [19]. For example, fewer residents receive vaccination or blood pressure monitoring in care homes [9]. In one large study of American nursing homes, diabetes, dementia, cancer, heart failure, renal failure, chronic pulmonary disease, and anemia were all associated with an increased risk of mortality at 12 months [20]. Older people living in care homes are susceptible to infections, particularly pneumonia [21–23], and are at risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infections [24, 25].

Having diabetes is associated with twice the risk of admission to a care home [2], and diabetes accounts for 12.3% of all admissions to care homes [26]. Disability associated with diabetes is characteristically progressive [27]. Residents with diabetes are likely to be at greater risk of microvascular disease [28] and visual impairment: 80% have cataract and 2.1% have diabetic retinopathy [29]. In the UK and the USA residents with diabetes are younger and at increased risk of hospital readmission, cognitive impairment, limb amputations, and death compared to non-diabetic residents [13, 30]. Pressure ulcers are more common in people with diabetes: in one prospective study (n = 14 607) the odds ratio of developing a pressure ulcer was 1.4 (95% CI 1.2–1.8) after adjusting for other co-morbidities [31].

In addition, residents with diabetes have a range of other co-morbidities and geriatric syndromes. Cognitive impairment and dementia are common in older people and are often the reasons people are admitted to a care home [32, 33]. One recent study of diabetes prevalence found the highest rates of undiagnosed diabetes in elderly mentally infirm (EMI) residential care homes [15], and the diabetes care for these residents in particular did not meet local and national standards. The impact of co-morbidities on diabetes care warrants further study. For example, cognitive impairment may result in residents being less able to monitor their blood glucose levels or inject insulin; Parkinson's disease is associated with increased cost of diabetes care by up to 300% [34].

Obesity is a risk factor for diabetes. In one US study, the proportion of obese residents newly admitted to care homes rose from 15% to 25% over a 10-year period [35]. Obesity in middle age is associated with a 30% increased risk of admission to care homes after 25 years [33]. The associated risk of diabetes may explain some of the increasing diabetes prevalence in US care homes [34]. However, care home residents with diabetes are often under- or malnourished, with half of all participants in one study receiving lower dietary energy intakes than recommended [36]. In another study, switching residents with diabetes to the "normal" diet provided in the care home did not cause any significant deterioration in glycemic control [37].

Hypoglycemia is the most common complication associated with older people with type 2 diabetes using glucose-lowering medicines and is common and most likely under-recognized in care homes [38]. For example mild hypoglycemic episodes are rarely recognized or documented, yet they contribute to future severe hypoglycemia because they impair the counter-regulatory response to hypoglycemia. Hypoglycemia risk factors are prevalent in care homes and include:

- older age
- using glucose-lowering medicines, especially insulin and some sulfonylureas: in fact, insulin is a predictor of hypoglycemia

- inappropriate focus on achieving tight blood glucose control rather than setting blood glucose targets that are safe for the *individual*
- multiple diabetes complications and co-morbidities
- renal impairment
- liver disease
- cardiovascular disease: hypoglycemia can provoke vascular events such as myocardial infarction and stroke
- cognitive impairment
- hypoglycemic unawareness, which is associated with a diminished counter-regulatory response to falling blood glucose levels and changed symptomatology such that neuroglycopenic symptoms predominate and are mistaken for other causes
- recent hospital admission
- recent hypoglycemic episode and history of hypoglycemia
- under-nutrition
- acute illness
- swallowing difficulties
- associated conditions such as cancer
- polypharmacy: older people are prescribed a mean of eight medicines, range 0–40 [18]
- care-home-related factors, including policies and processes such as timing of meals in relation to administering insulin and sulfonylureas, missed meals, availability of "hypo packs", using top-up insulin doses to treat episodes of hyperglycemia, policies concerning administration of glucagon, infrequent blood glucose monitoring, and the knowledge and competence of staff administering medicines (administering and managing medicines is complicated in care homes and there are many interruptions and competing demands on staff during medicine administration rounds, which exacerbate inadequate training and staffing levels [39]).

25.5 Common management problems

Some common clinical management problems that arise in the care of older adults living in care homes are summarized as follows:

- *Nutrition*: Weight loss and nutritional deficiency can occur through anorexic symptoms and reduced calorific intake. Other contributing factors include severe physical and cognitive impairment, as well as neurological and gastroenterological disorders associated with dysphagia, including stroke. In the future, increasing numbers of residents are also anticipated with obesity and associated problems, thus exacerbating function and mobility. Under-nutrition is associated with sarcopenia, frailty, and falls.
- *Increased risk of hypoglycemia*: Hypoglycemia can occur in residents receiving sulfonylureas or insulin through several predisposing factors described in the list above. Hypoglycemia is a significant falls risk, yet it rarely appears on falls risk tools.
- *Hyperglycemia and its consequences such as infections*: Recurrent skin, chest, and urinary infections may occur, especially if the control of blood glucose is not optimal. Infections themselves predispose the resident with diabetes to marked hyperglycemia or metabolic decompensation: ketoacidosis and hyperosmolar hyperglycemic states. Inappropriate top-up and supplemental doses of insulin are often used reactively to treat episodes of hyperglycemia despite the lack of evidence for their clinical benefit and safety [40]. They are usually reactive and do not treat the underlying cause of the hyperglycemia or adjust the medicine doses/type/regimen to prevent future hyperglycemia. Top-up insulin doses lead to hypoglycemia, rebound hyperglycemia and adverse glucose variability [40]. Supplemental doses might be appropriate in some circumstances, for example as part of an individualized sick-day care plan.
- *Urinary and fecal incontinence*: Urinary incontinence may be secondary to hyperglycemia-related urinary infection, poor mobility and/or cognitive impairment. It contributes to dehydration and falls risk. Fecal incontinence can be present in some residents due to diet, medicines, reduced fluid intake, and inactivity.
- *Pressure ulcers and leg or foot ulceration*: These can deteriorate and/or become infected and lead to a hospital admission. They compromise mobility and can be painful.
- *Communication difficulties*: These can lead to unrecognized diabetes care needs. Predisposing factors include cognitive impairment, dysphasia and dysarthria from cerebrovascular or other neurological disease, and sensory impairments such as visual and hearing loss and cognitive changes. Communication difficulties can also arise when residents do not speak the dominant language in the country and/or have low health literacy. Likewise, staff may not be skilled at

communication with older people or make allowance for age-related effects on memory and learning.

- *Cognitive impairment and dementia*: Dementia is associated with diabetes and is a common reason for admission to a care home. It affects all aspects of a person's life. An estimated 35.6 million people worldwide had dementia in 2010 and the number is expected to almost double every 20 years. Much of the increase will occur in developed countries [41]. Dementia poses particular care challenges such as food intake, managing medicines, continence, and safety for the resident and sometimes staff.
- *Increased risk of medicine errors and adverse events*: These can occur because residents are often taking multiple medicines to manage diabetes and other coexisting diseases. Risks can be exacerbated by infrequent review of medication and inadequate monitoring of blood glucose, renal, and liver function. Polypharmacy is a significant concern in care homes: rates between 39% and 65% are reported [42–44]. Admission to hospital is often associated with commencing a new medicine that may be appropriate at the time, but which is not stopped when it is no longer required. Undertaking a medicine-related adverse event risk screen can help avoid medicine adverse events [44].
- *Falls*: Many individual-related, organization-related, and policy-related factors contribute to falls. Factors that increase the risk of falls include being ambulant with a gait aid [45].
- *Pain*: Pain is often unrecognized and inadequately treated. It is due to a number of causes and can be physical, psychological or both. Regular pain assessment using appropriate pain assessment tools is an important part of care.

25.6 Organization of diabetes care in residential settings

25.6.1 Setting standards for diabetes care

Quality indicators provide insight into the quality of care, which is associated with quality of life, in aged-care homes [45]. Care home operators increasingly seek and are expected to offer quality care that focuses on the needs of individual residents and is person-centered (individualized care). In addition, the increasing emphasis on quality care is part of a wider consumer movement to a market-orientated model of health care [46].

Several countries have assessment instruments and minimum data sets, some of which are mandated in care homes. The American Diabetes Association (ADA) reviews its clinical practice recommendations annually, and these are comprehensive and up-to-date [47]. In the UK, the National Institute for Health and Clinical Excellence (NICE) and the National Service Framework (NSF) for diabetes identify the key components of diabetes care [48, 49], and similar guidelines are available from other organizations and in other countries. In the UK, the introduction of standards has been credited with improvements in health care, especially when linked to payments to general practitioners through the Quality and Outcomes Framework (QOF) [50]. The diabetes NSF identified a series of standards to be applied to the care of children and adults with diabetes which had little relevance or implications for residents of care homes. More recently, the adult social care outcomes toolkit (ASCOT) was developed to aid routine quality monitoring in the UK [51]. These processes and tools may not be directly applicable to other healthcare organizations in different countries.

In Australia, the Residential Care Quality Assessment tool assesses 24 areas of care to determine whether a care home meets accreditation standards. The tool was designed to complement the Aged Care Funding Instrument, but it is not mandated at this time [45], although Australian care homes do not receive funding if they are not accredited and they must meet minimum standards to be accredited. The outcomes of accreditation reviews are available on the accreditation agency's website. Importantly the assessment process does not focus enough on clinical outcomes [45].

Also in Australia, the Guiding Principles for Medication Management in Residential Aged Care Facilities document helps care homes address important medication-related quality issues such as polypharmacy and audit processes [52]. The document is consistent with quality use of medicines (QUM), which is one of the central objectives of the Australian National Medicines Policy (2000) and focuses on the judicious, appropriate, safe, and effective use of medicines [53]. However, for QUM to be a reality in care homes nurses, doctors, and pharmacists must consider therapeutic alternatives to medicines if possible, given that QUM advocates for using non-medicine options before medicines when it is safe and beneficial to do so.

Recently the National Residential Medication Chart was released to improve medicine safety and reduce administrative burden on prescribers, pharmacies, and aged-care staff in aged-care homes [54]. Although the chart was tested during its development and purports to have a holistic resident focus, reduce medicine-related incidents, set a standard for medicine use, and improve compliance and cost-effectiveness, it has not been widely evaluated in everyday use to date.

Care home managers must ensure staff administering medicines are competent and understand their role and responsibilities in relation to:

- residents self-administering medicines
- monitoring beneficial and adverse effects using blood glucose monitoring and other biochemical investigations, screening, and observation assessments
- managing nurse-initiated medicines
- using dose administration aids and insulin-delivery devices correctly
- testing blood glucose and interpreting the blood glucose pattern when managing medicines
- understanding which medicines should not be crushed
- storing and disposing of unused medicines safely and appropriately
- recognizing medicine safety issues/risks, such as hypo- and hyperglycemia and postural hypotension, and their consequences, such as confusion and falls, and other PRN medicines prescribed for pain, sleep management, and bowel function.

The McKellar Guidelines for Managing Older People in Residential and Other Care Settings describe current best practice diabetes care [55] and are being implemented as policy in some care homes. The authors are currently developing diabetes-specific clinical indicators to complement the guidelines.

Appropriate standards of care should be considered, where feasible, with specific concerns for diabetes in frail, older care home residents. The common clinical problems in this group, which may not occur in younger adults with diabetes, are listed in Table 22.2. For example, there is an increased likelihood of undernutrition, risk of hypoglycemia, and recurrent urinary infection in older people. Immobility is associated with the risk of ulceration of the lower limbs, buttocks, and heels, and impaired healing. Falls are a significant risk as functional status declines. The practice in hospitals of immobilizing patients to prevent falls may actually increase the falls risk by contributing to muscle wasting and weakness.

Although both the ADA and the NSF include sections about adults living in institutions, these primarily relate to prisoners and not to care home residents. In response to such guidelines and standards, health services are bound to develop policies to implement change, and the danger of using such inappropriate standards has been highlighted as vulnerable older people may suffer in the absence of targets specific to their needs [56]. However, they can also act as important audit tools, allowing the priorities of older people to be highlighted. In one case study, a combination of national, local, and care-home-specific standards was used to develop an audit tool to evaluate services for older people [57].

The International Diabetes Federation (IDF) Global Guideline for Managing Older people with Diabetes identified a set of diabetes-specific quality indicators that aged-care staff can use as quality indicators to audit diabetes-specific care [58].

25.6.2 Developing standards for care homes

There are two main barriers to optimizing diabetes care in care homes. First, there are some clinical issues which are specific to older people and may not be included in local diabetes service design. Second, there are factors relating to the care home itself, for example there is a well-recognized lack of sufficient staff training with few opportunities for continuing professional development in diabetes [59]. There are high rates of staff turnover in many homes, compounded by a large proportion of unqualified staff with little experience or training to prepare them for caring for residents with diabetes.

There is often a lack of resources and staff time, catering services, and equipment. In addition, boundaries between medical and nursing and other staff responsibilities can be unclear and can be exacerbated by poor communication. Capacity to accommodate erratic eating associated with dementia and resident preferences is a significant problem, especially when medicines are also required and care home routines and staff are inflexible.

Staff preparing meals and supervising residents at meal time may lack a basic understanding of nutrition principles. Many still focus on the “diabetic diet”. Communication difficulties between staff and residents

may exist that prevent needs being met; these may be linguistic or cultural, or might reflect co-morbidities, including neurological problems. Restrictive professional boundaries may prevent healthcare professionals from having specific inputs into care homes, especially within the independent sector. Quite clearly, the establishment of national standards of diabetes care within care homes may be an important initiative to promote care within these settings.

There is a lack of diabetes-related experience and knowledge among care home staff, and appropriate education and training are needed to improve diabetes care. However, difficulties in providing education and training include a lack of staff training budget in many homes, which means staff rely on free advice and information, some of which might be provided by pharmaceutical companies that supply products such as continence pads to care homes, which clearly represents a conflict of interest.

Many care staff are young and unskilled, and older members of staff are often employed in part-time and care attendant positions with very basic training, usually to assist with ADLs. Many homes have a high staff turnover rate, with poor pay and conditions, which can lead to low staff morale. Nursing staff work a rotating shift system, which can lead to a poor continuity of care and often precludes attendance at training events. In spite of these difficulties, diabetes training and education are provided to homes by many local diabetes care teams. These are usually welcomed by care home managers, and their success seems to relate to good local relationships being established. It also requires the local diabetes team to feel responsible for these homes and to be authorized by their managers to provide education and advice.

In the UK, individual home proprietors and trade associations can help improve diabetes care. For example, the Independent Healthcare Association is the largest association in the independent sector, representing acute, psychiatric, and long-term care providers across the UK. By facilitating the promotion and dissemination of best practice, research reports, and quality control systems within care homes, they are well placed to liaise with care home owners, managers, and staff to support education and training initiatives.

In response to such concerns, Diabetes UK reviewed diabetes care in institutions and produced a guideline for care homes. The Diabetes UK guideline [60] synthesized available evidence to identify the clinical issues of particular relevance to care homes:

- lack of care plans and case management approaches for residents with diabetes
- inadequate nutritional guidance
- lack of specialist health professional input
- diabetes care not coordinated between primary and secondary care services
- inadequate review and poor metabolic control
- lack of diabetes knowledge and competence among staff working in care homes
- lack of structured education and training for staff.

Where education is available, it is often provided by diabetes educators and other health professionals with little knowledge of diabetes in older people. Consequently, such "text book" teaching does not prepare care home staff to manage issues such as changed hyper- and hypoglycemic symptoms and the complexities of managing medicines and meals for people with dementia, wandering and "sundowner syndrome".

In the USA Funnel and Herman examined the policies and practices in a group of 17 skilled nursing homes in Michigan [61]. Although the ADA and the American Association for Diabetes Education first developed guidelines for diabetes care in skilled nursing homes in 1981 [62], the authors carried out their review using the 1995 version of less-specific criteria derived from the ADA [21]. The homes studied were generally large (mean number of beds 137) and the number of residents with diabetes per home ranged from 1 to 46 (mean 19).

More recently, a European Working Party devoted a section of its evidence-based diabetes guidelines specifically to care homes [63]. Examples of evidenced-based recommendations provided in the European Guidelines are as follows:

- At the time of admission to a care home, each resident must be screened for the presence of diabetes. Level of evidence 2++; grade of recommendation B.
- Each resident should have an annual screen for diabetes. Level of evidence 2+; grade of recommendation C.
- Each resident with diabetes should have an individualized diabetes care plan with the following minimum details: dietary plan, medication list, glycemic targets, weight, and nursing plan. Level of evidence 2+; grade of recommendation C. In addition, the care plan should be based on proactive risk assessments such as for hypoglycemia, medicine-related adverse events, falls, and pain.

- Each care home with diabetes residents should have an agreed Diabetes Care Policy or Protocol which is regularly audited. Level of evidence 2++; grade of recommendation B.
- Optimal blood pressure and blood glucose management may help to maintain cognitive and physical performance for each resident with diabetes. Level of evidence 2+; grade of recommendation C (extrapolated data). Significantly, blood glucose targets and HbA1c should be relevant to the individual's safety, risk of hypoglycemia, and life expectancy [55, 58]. Blood pressure targets should not place the individual at risk of postural hypotension and falls [58].
- Each resident should have a plan for managing end of life [55, 58].

25.7 Improving care

Residents with diabetes in care homes should receive a level of comprehensive diabetes care commensurate with their needs. The care should be on an equitable basis with people with diabetes who live in the community. The most important objectives are the following:

1. Where possible the care plan should be decided with the resident and/or their families, considering their individual quality of life indicators, which might not be assessed using current quality of life tools. Patent-generated quality of life tools might be more appropriate. Life expectancy and preparing for end of life is important: most people in care homes receiving a high level of care have a relatively short life expectancy.
2. Maintain the highest degree of quality of life and wellbeing, without subjecting residents to unnecessary and inappropriate medical and therapeutic interventions.
3. Ensure the resident is safe.
4. Identify and manage pain.
5. Provide sufficient support and opportunity to enable residents to manage their own diabetes when it is a feasible and worthwhile, and sufficient support and education for staff to enable them to manage residents with diabetes.
6. Ensure a dignified end of life according to each resident's preferences.
7. Avoid the malaise and lethargy associated with hyperglycemia.
8. Minimize the risk of and actual hypoglycemia.
9. Promote the greatest level of physical and cognitive function.
10. Carry out regular reviews, including medicines, complication status, functional status, and quality of life and wellbeing.

The IDF have indicated that people over 60 are at high cardiovascular risk, and risk factors such as smoking, renal disease, hypertension, and hyperlipidemia should be managed [58]. The IDF highlight the need to individualize metabolic targets and to consider the person's functional status and life expectancy. The IDF HbA1c recommendations for metabolic targets are:

1. Functionally independent: 7–7.5% (53–59 mmol/mol) using relevant glucose-lowering medicines as indicated and not delaying insulin initiation when indicated.
2. Functionally dependent: 7–8% (53–64 mmol/mol).
3. Frail older people and those with dementia: Up to 8.5% (70 mmol/mol).
4. End of life: the focus is on comfort and quality of life; therefore blood glucose and HbA1c targets should suit the individual and aim to prevent the distressing symptoms associated with hyper- and hypoglycemia.

25.8 Nutrition in older residents with diabetes

Residents are likely to have several nutrition risk factors. These include staff lack of nutrition knowledge and outdated ideas about "diabetic diets". It is vital that up-to-date information about diabetes and healthy eating is provided to care home staff, especially those who are responsible for menu planning, food purchasing, and cooking. Local dietetic services can provide advice about implementing healthy-eating policies if the home does not have a visiting dietitian. They can help to train staff about the dietary aspects of caring for older residents with diabetes.

Commonsense processes such as ensuring the resident knows when meal times are, ensuring they can reach their meals, and flexibility when people with dementia eat at erratic times are important. Communal dining suits some people but some residents prefer to eat alone. It is extremely important that residents with particular needs, such as vegetarians and those with food intolerances, are catered for and that the meals are acceptable to the individual.

25.9 Responsibility of physicians

All residents of care homes in the UK are registered with a general practitioner (GP) and diabetes care is assumed to be delivered by GPs for the majority of patients. The increasing numbers of older people in care homes is having a significant impact on the workload of many GPs [64] and there is no recognition or encouragement for GPs to provide specialist diabetes care in residential settings. Many visits to care homes are reactive in nature, taking place only when a problem is identified by the home staff. Care home residents often have mobility problems, preventing them from visiting the GP's surgery for annual review, and few GPs provide a multidisciplinary annual review service in the care home.

Diabetologists often have little experience managing frail older people in care homes and geriatricians undertake less continuing and community care. Meanwhile, commissioning priorities for older people focus on the management of long-term conditions by community and other non-medical staff, concentrating on acute illness and preventing hospital admission. The transfer of long-term care from hospitals to care homes has not been accompanied by any significant transfer of medical resources to the community. In consequence, older people in care homes increasingly fall between primary, secondary, and social care services, and all too often their needs are forgotten [65].

Since some concerns about care home medicine in the UK were highlighted over 10 years ago [66], there have been no significant national developments and no clear model has evolved. At the time, a number of options were envisaged: visiting medical officers, dedicated geriatric medical and psychiatric outreach services, and integrated care by specialists, commissioned by primary care or a more formalized model of shared care between hospital and GP. Some studies have been conducted in the UK on chronic disease management using American-style health maintenance organizations (HMOs), but they have not gone as far as employing their own medical staff. Rather perversely, the Evercare project used a model of care devised and implemented in the USA for the care of nursing home residents, but applied it to frail older people living in their own homes, with no evidence of beneficial effect [67].

GPs are still responsible for the medical care of individual residents registered with their practice. There remains no formal structure for the routine involvement of consultants in geriatric medicine or diabetes, nor for other healthcare professionals to provide multidisciplinary diabetes care when required. In the absence of any formal national structure local, *ad hoc* arrangements are still being employed in an attempt to provide the best possible multidisciplinary care.

25.10 Multidisciplinary diabetes care

Well-coordinated multidisciplinary team care is essential for effective care of older people with diabetes, especially in care homes. Thus, efficient and well-organized referral processes, documentation, communication, and information sharing must be in place. The elements of multidisciplinary diabetes care include the following:

- There should be an individualized diabetes care plan agreed with each individual resident, when possible.
- The plan should include a series of individualized metabolic targets and an individualized nutrition plan.
- An annual review assessment should involve an eye check, a foot check, functional status check, mental health and cognitive status check, a medicines review, and a review of the end-of-life care plan.
- Support and assistance in diabetes care should be provided by a named person who will be involved in metabolic monitoring with the resident.
- In the UK all residents with diabetes should be included in the local diabetes register at GP and/or district level, as appropriate.

These elements may be provided by a number of healthcare professionals. The diabetes NSF in the UK covers all of these, but the targeting of aged-care homes is not well addressed, and there is a risk that QOF returns are not submitted for some of the more challenging tasks, resulting in older people being excluded from care.

25.11 Nursing care

25.11.1 Diabetes specialist nurses

Diabetes specialist nurses/diabetes educators have special training and education in diabetes and are an invaluable link between primary and secondary diabetes care for older people [68]. They can provide a high-quality service to older people with diabetes [69] provided their education includes the changes

associated with increasing age and the effects of age and diabetes on pathophysiology, functional status, and care needs including medicine uptake, distribution, metabolism, and excretion. Increasingly, diabetes specialist nurses are employed to work in the community and, within the time constraints of their busy jobs, may become involved in diabetes education and support for home care staff, assisting in the development of diabetes care policies for the home and individual care plans.

25.11.2 Primary care practice nurses

Increasingly, in some parts of the European Union practice-based nurses who have had special training in diabetes are coordinating diabetes care in general practice. They may also be empowered to visit residents of the practice who are living in care homes to assist in the delivery of the care objectives outlined above. This may not apply to many other parts of the world.

25.11.3 District (community) based nurses

District nurses can play an immense supporting role in diabetes care in residential settings, despite many receiving little, if any, special training in this area. The major remit of the district nurse is in the provision of nursing support to residential homes, including advice to staff on diabetes care. They often administer insulin to residents unable to self-inject because of physical impairment, cognitive disability, or behavioral disturbance. Specific arrangements can be made between care homes and district nursing services with the delegation of specific diabetes care tasks to care home staff. However, care homes have been criticized over recent years for their medicines management policies, with insulin having attracted particularly heavy criticism [70]. There can also be tensions when the resident's personal care needs alter to a point where they require nursing rather than personal care, with an expectation that the care home nursing staff will offer monitoring and insulin therapy.

25.12 Foot care

Published information from many countries worldwide testifies to the high prevalence of diabetic foot disease among the residents of care homes [71–73]. The risk of *foot ulceration* is increased in those with advancing age, loss of protective pain sensation due to diabetic peripheral neuropathy, peripheral vascular disease, and bony foot abnormalities. Although residents should have access to free care from state-registered podiatrists, in some homes private podiatrists are employed to offer routine foot care, and residents maybe encouraged to pay fees for their foot care. Thus, a local state-registered podiatrist with an interest in diabetes is a very important member of a local multidisciplinary diabetes team, and his or her skills need to be utilized by care home staff in appropriate ways.

All people with diabetes should have an annual foot examination as part of the review process, and residents in care homes are not exempt from this recommendation [48]. This examination is to detect feet at risk of ulceration. At its simplest, this involves a brief history to discover any previous episodes of ulceration, an inspection of the feet to check for bony abnormalities, palpation of the dorsalis pedis and posterior tibial pulses to detect ischemia, and the use of a 5.07 g nylon monofilament to detect the loss of protective pain sensation. This foot examination can be carried out by any member of the community diabetes team who has the relevant skills and experience and if the foot is deemed to be at risk it should be checked every 3 months by a podiatrist. It is also important to train care home staff to understand the importance of preventive foot care and to alert them to the importance of detecting early signs of foot ulceration and infection so that urgent prompt referral and action can be taken. The local state-registered podiatrist with an interest in diabetes will usually be the best person to provide this help.

25.13 Eye care

A lack of specialist eye care and regular ophthalmology review of residents with diabetes has been demonstrated in UK care homes [72]. Many older people with diabetes have undetected refractive error, and screening of immobile residents in care homes is feasible, but costly [74].

The national standards for eye-screening programs in the UK are established, including exclusion criteria [75]. Some screening programs are based on examinations carried out by experienced and specially trained optometrists, which allows refractive error, glaucoma, and cataract to be assessed at the same time as screening for diabetic retinopathy. The national standard is for

diabetes eye screening using digital photography of the retina. However, immobile patients are excluded, which argues that they are unlikely to receive retinal surgery.

The barriers to optometrists working in care homes include:

- the funding of retinal screening at the exclusion of eye examinations in care homes
- no financially viable option for self-employed optometrists.

Eye care for care home residents could be improved by adequate funding of optometric assessment by contractual arrangements with the local commissioners, resulting in:

- improved and regular access of optometrists into care homes
- visual screening of all new admissions who have diabetes.

This would require:

1. improved facilities at each care home to allow full optometric assessment
2. education of care staff about visual health in residents
3. the identification of a member of the care home staff responsible for organizing optometrist visits
4. improved referral systems for residents with eye problems to specialist secondary care.

25.14 Assessing the efficacy and efficiency of diabetes care

Outcome measurements for diabetes in primary care have been incorporated into the audit tools supporting the NSF [48], and some of the gaps relating to the care of older people are outlined in Table 25.2. A uniform, comprehensive, standardized assessment for the routine long-term care of older people, the minimum dataset–resident assessment instrument (MDS-RAI), has been introduced into all nursing homes in the USA and Iceland, and also in three provinces in Canada. A US research group has combined data from the MDS-RAI instrument with other available data from Medicare and hospital discharge to study treatment effects using valid measures of outcome in this frail population [76]. More recently, similar assessments have been carried out in the UK to assess nursing care needs [77].

A number of national and international outcome measures are available for older adults with diabetes [63, 72], but these have not yet been adequately tested in care home settings. The purpose of outcome measures in care homes is to:

Table 25.2 Management problems in care homes.

Nutritional deficiency and weight loss
Increased risk of hypoglycemia
Infections
Urinary and fecal incontinence
Pressure ulcers
Leg and foot ulceration
Communication difficulties
Geriatric syndromes, including frailty
Polypharmacy and the associated increased risk of medicine-related errors and adverse reactions
Planning for end-of-life care

- assess the quality of care delivered to each resident with diabetes
- assess the impact of diabetes on each resident in terms of personal wellbeing, functional disability, and rate of diabetes complications
- determine the impact of use of care home resources for residents with diabetes in terms of use of care staff time, dietary planning, monitoring equipment, and educational initiatives.

The potential outcome measures are summarized in Table 25.3. The data collection must be carried out by care staff and visiting healthcare professionals, and must represent the common objectives of diabetes care for all parties.

25.15 What care homes need to provide

In order to sustain effective diabetes care, care homes need to provide a suitable care environment in terms of staff, resources, equipment, and facilities. These should include:

- staff who receive appropriate training and education in the basic management of diabetes in care home settings and the particular differences in older people
- facilities to carry out blood glucose monitoring and staff trained to use the equipment, interpret the results, and use them in care planning

Table 25.3 Outcome measures for use in care home diabetes care.

1 The percentage of residents achieving agreed metabolic targets of HBA1c, blood pressure, and weight during previous 12 months
2 Frequency and severity of hypoglycemic episodes in previous 12 months
3 Frequency and severity of painful episodes in previous month
4 Frequency of hospital admissions for diabetes-related problems in previous 12 months
5 Complication rates of visual loss, foot ulceration, renal impairment, falls, and angina
6 Changes in level of dependency and physical and mental function using the Barthel ADL (or extended ADL measures) and Mini-Mental State Examination Score (MMSE) during previous 12 months
7 Health-related quality of life and wellbeing of each resident with diabetes (e.g. using the SF 36 or sickness impact profile measures); changes from admission to now, or changes within previous 12 months
8 The percentage of patients with completed diabetes care plans and annual reviews in the past 12 months that also include end-of-life planning as appropriate
9 Regular assessment of staff knowledge and skills competency

- accommodation for and annual review of complication status such as foot care, co-morbidities, medicines, quality of life, and planning for end-of-life care.
- a member of catering staff familiar with dietary planning for residents with diabetes
- a protocol of diabetes care agreed by the staff of the home, visiting diabetes healthcare professionals, and the GP, which should be evidence based, focus on safety and risk minimization, include the need to personalize care plans, which should be developed with the resident where possible
- a method of collecting agreed diabetes outcome indicator data
- sufficient staff members trained to manage medicines, including administering insulin
- educational resources on diabetes for residents and their families
- access to transport to enable residents to receive specialist treatment off site
- an admission policy that includes a strategy for those with known diabetes and screening for diabetes in undiagnosed older people.

Aspray *et al.* [57] demonstrated that using a combination of standards (generalized and age/environment specific) can achieve appropriate service changes.

25.16 What needs to be provided in near-patient healthcare settings

Local diabetes services must encompass the special needs of care home residents with diabetes, including support and guidance for homes. In the UK, for example, the general funding of care in residential and nursing homes will remain a subject of continued government debate for the foreseeable future. The joint commissioning of health and social services for older people would be a great step forward. Diabetes contracts within this context would support high-quality care for residents of care homes, and should include:

- optometric services providing both on-site and clinic-based eye services
- podiatry services with time specifically dedicated to care home residents
- agreed criteria for referral to secondary and intermediate care specialist services
- at least one diabetes specialist nurse specifically responsible for older people who would play a prominent role in the effective organization and delivery of diabetes care to care homes in the area, including diabetes education
- at least one community dietitian in each locality, responsible for dietary and nutritional support of residents
- the registration of all care home residents with diabetes on diabetes registers to ensure that they are involved in diabetes clinical audit projects
- diabetes educational and training programs for care home staff at local, regional, and national level to ensure that staff are kept up to date
- processes for auditing care services.

25.17 Conclusion

Older people in care homes are vulnerable. They usually have several diabetes complications, and other co-morbidities and polypharmacy are common. Deficiencies in care are well documented. Diabetes care in residential settings has not attracted a great deal of scientific clinical enquiry, consequently information about the quality of diabetes care delivered and the outcomes of care in care homes is just emerging. The significant morbidity and disability of residents with diabetes within care homes

and many receiving community care poses many complex and challenging problems for all healthcare professionals involved in delivering diabetes care and significantly for health service planners and funders, given longer life expectancy and prevalence of diabetes in older age. Some possible practical strategies to improve diabetes care have been proposed in this chapter.

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CHAPTER 26

Primary and community care of diabetes in older people

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KEY MESSAGES

- In recent years there has been a significant shift from secondary to primary care delivery in many countries.
- Multidisciplinary care is required for optimal management of diabetes in the community.
- Care must be individualized in terms of setting appropriate glycemic, blood pressure, and lipid targets and choice of medication.
- Older patients may have significant co-morbidities or reduced life expectancy that alters the risk–benefit balance of aggressive management of cardiovascular risk.
- Issues such as polypharmacy, mental illness, risk of falls, frailty, urinary incontinence, social isolation, and medication adherence all need to be considered as part of the management plan.

26.1 Introduction

The proportion of the community in older age groups is rapidly changing. For example, in Europe the proportion of the community aged 65 years and older has been projected to grow from just under 15% in 2000 to more than 23% by 2030 and the proportion of those aged 80 years and older has been estimated to more than double over the same time period from 3% to 6.4% [1]. This trend is occurring not just in more developed countries: current projections suggest that by 2050 78% of all people in the world over 65 years of age will live in less-developed regions [2].

The prevalence of type 2 diabetes increases with age, usually peaking around the age range of 65–74 years. In the USA the rate of diagnosed diabetes in people aged 65–74 years is 21.8% [3] while over 26% of those between 60 and 69 years in England, Wales, and Scotland have had a diabetes diagnosis [4].

Although older people with diabetes are at risk of the same range of macrovascular and microvascular complications of diabetes as those of a younger age, the absolute cardiovascular risk is much greater at more advanced age. Older individuals with diabetes experience greater morbidity and mortality than those without diabetes [5] and have higher risks for polypharmacy, cognitive impairment, depression, falls, urinary incontinence, impaired mobility, and persistent pain [6]. Optimally managing these co-morbidities and risks requires a broad range of health practitioner expertise and is ideally suited to a primary health environment.

Along with an increasing prevalence of diabetes is an increasing number of people developing diabetes at earlier ages, resulting in an increased number of complications and co-morbidities needing to be managed for an increased number of years.

These trends make it inevitable that in all countries economic and health workforce resources will come under increasing strain as a result. Consequently, systems of care need to evolve in order to cope with this increasing diabetes population, and in many countries this has already resulted in a shift in care status,

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from secondary to primary. Along with managing those already diagnosed with diabetes, primary health practitioners are best placed to advise and assist their patients in relation to those lifestyle behaviors most likely to prevent or delay the development of type 2 diabetes.

26.2 Definition of primary care

Primary care cannot be unambiguously defined as a fixed organizational structure or level of care. It has been suggested that it is best considered to be a composite of five essential characteristics [7]:

1 Care that is easily accessible, without financial or geographic barriers, within the community.
2 A focus on person-oriented rather than disease- or body system-oriented care, with continuity of care as a key component.
3 Comprehensive, evidence-based generalist care for all common health problems, collaborating with specialist services when required.
4 A public health perspective that includes attention to the social determinants of health and strong collaboration with public health and social services.
5 Partnership in which patients are seen as active participants in managing their own health, including shared decision making.

While the importance of primary care is now generally accepted as central to providing more equitable, inclusive, and affordable health care [8], there is a large variation in the strength of primary care across different countries [9]. While different models of primary care exist, the roles and functions of primary care are converging. However, there is still a large variation in the organization, structure, and funding base of primary care between countries and no country can claim to have a primary care system that adequately addresses all current and emerging health challenges, including the care for older people with diabetes.(7)

The boundaries of primary and secondary care also differ between and even within countries and in many health systems. The primary care–secondary care interface and the boundaries between primary care and hospital specialist care are dynamic and changing [10]. In many countries, organizational structures are changing and in some cases have led to integrated structures comprising primary and secondary care. Many roles traditionally provided by secondary care specialists are now being managed by members of the primary care team. In Europe, for example, specialist outpatient care has increasingly shifted to primary care through outreach clinics and some inpatient services traditionally provided by specialists in hospital have shifted to primary care through hospital-in-the-home arrangements [11, 12].

The World Health Organization considers that the term "primary health care" is based on principles of equity, participation, intersectoral action, appropriate technology, and a central role played by the health system [13]. Primary care then is more than just gate keeping. It is first contact, accessible, comprehensive, coordinated, and care continued over time. Within this framework, general practice is synonymous with primary care and family medicine. However, primary care teams vary between and within countries in composition and organizational model, and because they are by definition patient-centered, their composition and model can vary over time. A core primary care team usually includes a general practitioner (GP) and a nurse, but larger teams can comprise up to 30 professionals, including community nurses, midwives, dentists, physiotherapist, social workers, psychologists, psychiatrists, social workers, dietitians, pharmacists, speech therapists, podiatrists, and administrators [13].

26.3 The shift of diabetes care from the hospital to the community

Until recently most diabetes care was managed largely by specialists, often in large hospital-based outpatient clinics.

In the last 40 years, in the UK, Australian, and Canada and in many countries of Europe, people with diabetes, particularly type 2 diabetes, began to be managed more and more in primary care [14–16]. This came about usually by necessity as the burden of diabetes outstripped specialist and secondary care capacity. Sometimes this occurred in a systematic, planned, and agreed manner, and sometimes without adequate consultation or upskilling of the primary care workforce.

There is evidence demonstrating the effectiveness of community-based care for diabetes compared to hospital-based care. When care in general practice was shared across a team of health practitioners using computerized reminder systems, HbA1c levels were lower in general practice and continuity of care was greater in general care with fewer patients lost to follow up [17, 18].

In contrast, community-based care with less-developed support systems showed evidence of worse outcomes. A review in 1998 of five studies looking at the differences between community and hospital care found that unstructured community care was associated with a range of poor outcomes, ranging from poorer follow-up and glycemic control to increased mortality when compared to hospital care [17–19]. A randomized controlled study comparing hospital care to general practice care without any systematic recall system showed increased medical admissions, increased deaths, and higher HbA1c in the general practice group [20]. However, the meta-analysis established that a computerized recall system in a general practice setting can achieve standards of care as good as – or even better than – hospital outpatient care, at least in the short term [18].

In individual countries access to primary care and to specialist care can vary significantly. The limited capacity of hospital services to cope with the increasing demand for care of people with diabetes is, as has been mentioned, a common scenario. In other environments, a relative or absolute lack of primary care resources can be the main issue determining location of diabetes care for elderly people with diabetes. A detailed comparison of access to health care for older people in England and the USA, for example, found that for people over 75 years of age access to revascularization procedures was much greater in the USA but access to primary care was much better in England [21].

26.4 The primary care diabetes team

Primary care is now well established as a multidisciplinary team-based approach to healthcare delivery. No individual health professional can adequately and optimally provide the complex combination of services, starting from prevention and then managing glycemia, cardiovascular risk factors, co-morbidities, frailty, and disability, that is required by older patients with diabetes [7].

The individual team members comprising primary care diabetes teams also vary enormously between and even within individual countries. Issues affecting the availability of different team members include whether services are funded by patients themselves, by health insurers or by government, the availability of an individual health practitioner workforce, and whether services are required in urban or rural areas.

In an ideal situation, a team might include a GP, diabetes nurse or educator, a practice nurse, dietitian/nutritionist, podiatrist, optometrist/optician or ophthalmologist, exercise physiologist/physiotherapist and a psychologist/counsellor. Sometimes other team members, such as a pharmacist or medical specialists, may also be required. Even if available, not all team members are required for each patient at any point in time (Figure 26.1).

The central role of an ongoing relationship with a primary care physician or GP is well established and associations have been found between physician–patient continuity and patient satisfaction, reduced hospital service utilization, increased efficiency, and improved participation in preventive care activities [22–24]. However, a GP may not always be the best person to provide the care co-ordination role and such care co-ordination may be better performed by practice or community nurses [25]. The establishment of effective integrated primary care services has often been adversely affected by failure of committed participation of key members when GPs have not had central roles in developing these services and where the models have been developed in hospital settings or where coordinators have been based in emergency services or home-based nursing services [26–28]. Ideally, care coordination case managers should be co-located with GPs [7].

It is recommended that primary care teams working with older people with diabetes should have well-structured protocols for shared care with agreements on management of new cases, criteria for hospital admission, access to specialist services, and follow-up [29]. Examples of criteria for referral to hospital specialist care should include [29]:

- patients with severe vascular complications
- patients who require treatment for diabetes eye disease, foot ulceration or nephropathy
- patients with increasing dependency and immobility
- patients with unstable cardiovascular disease
- patients with poor metabolic control where it is proving very difficult to control HbA1c, lipids or blood pressure to agreed targets.

In some countries financial incentives are provided for providing good-quality care for people with chronic diseases. Payments may be made when processes of care are shown to reach a pre-specified standard or for the achievement of good quality care in specific areas [30–37]. In diabetes, “pay for performance” systems can

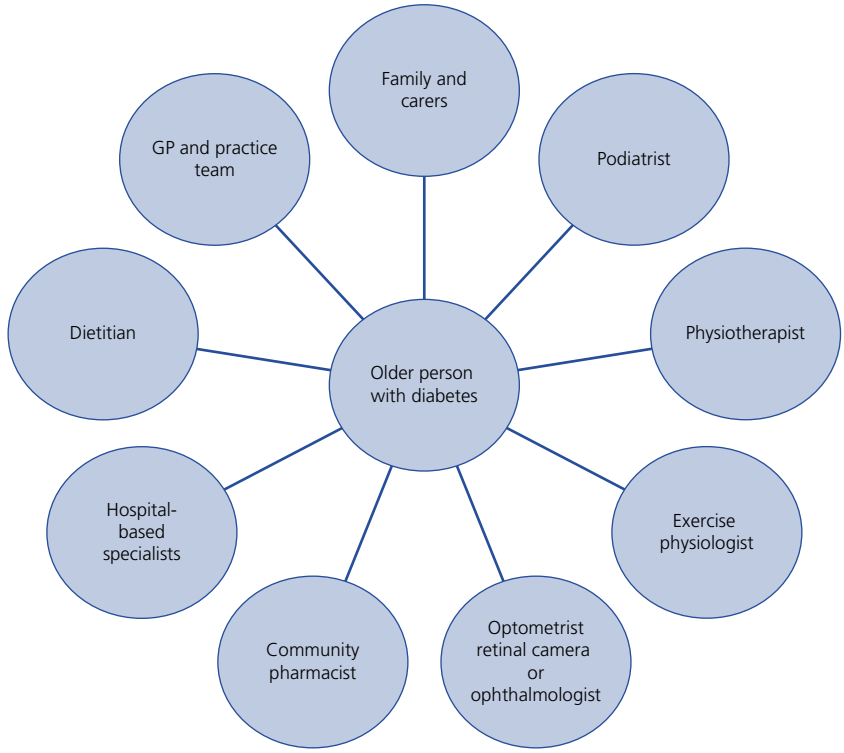

Figure 26.1 Healthcare professionals involved in the care of older people with diabetes in the community.

reward the achievement of pre-specified target levels of blood pressure, HbA1c levels, and lipids in a pre-specified percentage of patients. Although a number of pay for performance incentive schemes have been launched in the USA, the best-developed is in the UK, where it is referred to as the Quality and Outcomes Framework. In this system, points are achieved for both process and outcome achievement; the points then attract a payment figure which depends on the number of patients in the practice and the square root of the disease prevalence [38–40].

26.5 Individualizing management

Older people with diabetes managed in primary care are a very heterogeneous group ranging from those living independently in the community to those in aged-care facilities requiring full-time care. Their general health status can also range from fit and active to frail with many disabilities and co-morbidities. With the increasing proportion of the population in older age groups, chronic diseases, such as diabetes, and multiple morbidities are expected to become increasingly prevalent [41]. In people over 65 years prevalence of multimorbidity has been reported as varying between 50% and 80% and in those above 80 years of age prevalence of more than 70% has been reported [42–45]. Primary care teams and GPs are ideally placed to deal with multiple co-morbid physical and mental health conditions in a coordinated way.

The broad goals of diabetes management in older people are not significantly different from those of younger people with diabetes. Safely controlling glycemia and management aimed at reducing the other risk factors for macrovascular and microvascular disease remain paramount. However, particularly in frail elderly people with diabetes, the risk–benefit analysis of various interventions is often far more complicated, requiring good communication between primary care team members and often also with those involved in secondary care. In frail elderly people with diabetes, avoidance of hypoglycemia, hypotension, medication interactions, and worsening of other co-morbidities can often be more important than tight control of individual

cardiovascular risk factors. It is also important to remember that excessive hypoglycemia or hyperglycemia can further exacerbate pre-existing cognitive impairment [46]. The primary care practitioner is also required to carefully manage a significant number of co-morbidities that can affect quality of life and a patient's ability to optimize their self-care of diabetes and other conditions [46].

Balancing the benefits of achieving glycemic, blood pressure, and lipid targets in elderly patients against the often increased risks of medication adverse reactions, hypotension, and hypoglycemia can be complex and challenging. Appropriate targets for these cardiovascular risk factors and other parameters need to be determined on an individual basis at a particular point in time and reviewed often to consider additional factors that might change the appropriate target such as increasing frailty, development of new co-morbidities, and changed home or social circumstances.

26.6 Glycemic targets

Although elderly patients are often included in large diabetes trials, those studies specifically targeting elderly people with diabetes are more often observational than randomized and placebo-controlled. Nevertheless, relationships between poor glycemic control in elderly patients and increased mortality [47–50], cardiovascular events [51, 52], and retinopathy [53, 54] have been identified in these studies.

In the UK Prospective Diabetes Study (UKPDS) of glycemic control [55], newly diagnosed patients with type 2 diabetes were enrolled up to the age of 65 years and followed for a mean of 10 years. The intensively treated group attained a mean HbA1c of 7% compared to the standard control group (mean 7.9%). This 0.9% reduction was associated with a 12% reduction for any diabetes-related endpoint, and a 25% reduction in microvascular endpoints. There was also a 16% reduction in macrovascular events, which just failed to reach the level of statistical significance. On this basis it could be suggested that there is an evidence base for tight glycemic control up to the age of 75 years. Interestingly, after completion of the UKPDS trial all surviving patients entered a post-trial monitoring program for another 10 years [56]. Baseline differences in HbA1c were lost by 1 year but reductions in microvascular disease in the originally intensively treated group were still evident at the end of 10 years post-trial monitoring. Differences in macrovascular outcomes also achieved statistical significance at this time, despite no active treatment in the intervening 10 years. Relative risk reductions of 24% for microvascular disease, 15% for myocardial infarction, and 13% for death from any cause were seen in the original intensively treated group compared to the original conventionally treated group [56].

There is little specific research to provide the basis of optimal glycemic targets for older people with diabetes. The risks of hyperglycemia and hypoglycemia in this age group make it imperative to individualize glycemic goals after considering the need for cardiovascular risk reduction, overall health, and projected life-span imperative. For elderly patients especially, glycemic targets may need ongoing adjustment. Factors to consider include patient attitude to diabetes, expected concordance with prescribed therapy, risks associated with hypoglycemia and other adverse reactions, duration of diabetes, life expectancy, important co-morbidities, established vascular complications, and patient support systems [57].

Adverse effects of treatment, particularly hypoglycemia, can increase the risk of falls and exacerbate co-morbidities, often with an impact on ability to maintain the same level of independence in community living. On the other hand, impaired vision [58–60] and cognition [61–65], and sometimes dehydration can accompany undertreated hyperglycemia. This can increase the risk of falls and functional decline in older patients with diabetes.

For those elderly people with diabetes who are fit and active with a life expectancy beyond 10 years, HbA1c targets of 7.0% are often still very appropriate. However, a goal of 8.0% may be more appropriate in those with long-standing diabetes, particularly if there is coexisting or high risk of cardiovascular disease because lower targets in this group of patients may be associated with increased mortality, as was seen in the ACCORD trial [6,66–70].

Diabetes medications that increase the likelihood of hypoglycemia need to be carefully measured against the significantly increased risks associated with hypoglycemia in older people with diabetes. Hypoglycemia in this group may lead to impairment in cognitive function and increase the risk of adverse cardiovascular events and cardiac autonomic dysfunction [71]. Recurrent severe hypoglycemia has also been associated with increased rates of dementia [72]. In frail elderly patients,

even mild hypoglycemia can have severe consequences if it results in falls, fractures, and loss of independent living.

A number of conditions commonly managed in primary care can sometimes make HbA1c levels inaccurate for monitoring glycemic control in older people with diabetes. These include anemia, recent blood transfusion or erythropoietin infusion, chronic kidney disease, recent acute illness, or chronic liver disease [73].

26.7 Lifestyle modification

Appropriate diet, loss of excess weight, and regular aerobic and resistance exercise continue to be beneficial in the majority of older people with diabetes. Individualization of advice in these areas is important, with due consideration given to co-morbidities and family and social supports. This is an area where the multidisciplinary input of a primary care team can be invaluable, particularly including a dietitian or nutritionist, diabetes nurse or educator, and exercise physiologist or physiotherapist. A randomized trial of specific dietary intervention in people with diabetes over the age of 65 years demonstrated significant improvements in both fasting blood sugar and HbA1c [74]. In the Diabetes Prevention Program, the greatest improvements in glycemia were seen in the oldest age group of patients, those over 60 years of age at baseline [75, 76]. This was at least partly related to better adherence to lifestyle advice.

Older patients with diabetes enjoy the same benefits from regular exercise as younger patients in terms of maintenance of physical function, reduced cardiovascular risk, and improved insulin sensitivity. However, for older patients there are extra benefits in terms of reduction in falls, depression, and arthritic pain, and in increased strength and balance, quality of life, and survival [77–80]. Patients at high risk for falls should be referred to primary care team members such as exercise physiologists or physiotherapists for falls prevention training focused on balance and muscle strengthening [81].

In obese older patients with diabetes, a modest weight loss target of 5% body weight through calorie reduction and increased exercise has been shown to be beneficial [6, 82]. It is important to carefully monitor weight loss in older people with diabetes because there can also be significant risks of increased morbidity and mortality associated with under-nutrition, especially in older patients [83]. Unexpected or involuntary weight loss in this group needs to be carefully assessed and monitored to identify other co-morbidities that may pose additional adverse health risks to these patients.

It is important to remember that the benefits of continuing to focus on appropriate lifestyle, supported by multidisciplinary assessment and advice, remains equally important in older people with diabetes as in younger age cohorts.

26.8 Pharmacotherapy

A recent review [84] of meta-analyses, randomized controlled trials and evidence-based reviews found there to be a relative lack of specific data looking at the choice of diabetic pharmacotherapy options in older patient groups, although most large diabetes drug studies have included some patients over the age of 65 years. The appropriate choice of therapy in older age groups requires very careful individualization, taking into account frailty, renal function, weight status, risks of hypoglycemia, cognitive function, home support systems, and co-morbidities, particularly chronic kidney disease, cardiac failure, liver dysfunction, and cardiovascular disease [84]. Primary care practitioners are ideally placed to appropriately consider these interacting factors in determining the most appropriate combination and doses of pharmacotherapy in older people with diabetes. Many guidelines for the treatment of diabetes in the elderly have as a central concept that doctors should base recommendations for treatment targets or interventions on life expectancy [29,70,85]. Patients whose life expectancy is limited (usually less than 5–10 years) are not considered likely to benefit from intensive glucose control, whereas those with longer life expectancy are more likely to benefit from more aggressive glycemic control. This is supported by the observation that the cumulative event curves for intensive and conventional glycemic control arms of the UKPDS separated after 9 years [67].

26.9 Screening for microvascular complications

26.9.1 Retinopathy

The prevalence of retinopathy increases progressively with duration of diabetes in both type 1 and type 2 diabetes with poor glycemic control and with younger

age at original diagnosis [55,86,87]. Retinopathy rates and severity have decreased with better screening, improvements in glycemic control, and better treatments for retinopathy [86,88–93].

Regular eye examination is essential in the primary care setting to detect any sign of retinopathy in order to refer for appropriate specialist care as early as possible to reduce the impact of retinopathy. Poor vision in older people with diabetes has many consequences, including increased risk of falls and accidents, social isolation, and difficulties with monitoring blood glucose and administering oral and injectable therapies.

Regular screening by optometrists or ophthalmologists from diagnosis and at least once or twice yearly according to the presence and severity of retinopathy and/or other eye disease is essential. These examinations also screen for and monitor cataracts and glaucoma, both more common in older people with diabetes.

26.9.2 Nephropathy

The prevalence of at least moderate albuminuria in people who have had diabetes for 10 years is at least 25% and in some studies up to 40% [88,94–97]. Prevalence rates show considerable ethnic variation, being higher in Asian and Hispanic populations [94, 95].

Since the advent of angiotensin-converting enzyme (ACE) treatments effective at reducing development and progression of nephropathy, screening at least annually for diabetic nephropathy has been generally been recommended as optimum routine care.

The prevalence of at least moderate albuminuria at the time of diagnosis of type 2 diabetes may be higher in older patients, making it essential to screen from the time of diagnosis [98]. There may be other causes for this higher prevalence, such as longer periods of undiagnosed diabetes or other coexisting conditions such as benign nephrosclerosis.

26.9.3 Diabetic foot disease

Foot pathology is the cause of significant morbidity in people with diabetes and the prevalence is much greater in older patients. Both vascular and neurological disease can contribute to the development of foot disease in people with diabetes. Additionally, many older people with diabetes have difficulty seeing or reaching their feet, making adequate self-inspection and foot care difficult or impossible.

Primary care teams are ideally placed to provide regular feet examination by GPs, practice nurses or podiatrists. This examination should also include assessment of patient ability to see and reach their feet and enquiry as to other family members or carers who might be able to assist with regular foot examination in the home. At least annually, detailed neurological examination and assessments for peripheral artery disease should be performed. Regular review by a podiatrist for those considered to be at high risk for diabetic foot complications is recommended.

26.9.4 Cardiovascular risk reduction

Both diabetes and age are major risk factors for coronary heart disease (CHD) so it is not surprising that CHD is the greatest cause of death in older people with diabetes. As well as glycemic control, risk reduction should address smoking cessation if relevant and good control of hypertension and dyslipidemia. As with glycemic goals for older patients, goals for hypertension and lipid management in elderly patients with diabetes should be individualized based on co-morbidities, life expectancy, cognitive state, and patient preference.

26.10 Smoking cessation

In patients with diabetes, smoking is an independent risk factor for all-cause mortality. Whenever possible, smoking cessation should be a priority in discussions with older people with diabetes. Smoking cessation even after the age of 65 years has been associated with reductions in mortality as well as significant improvements in a range of functional parameters [99].

26.11 Treatment of hypertension

It can be suggested that there is an evidence base for blood pressure lowering up to the age of about 80 years in people with type 2 diabetes.

In the blood pressure arm of the UKPDS study [100], 1148 people with hypertension and type 2 diabetes were randomized to a tight control arm or a less-tight control arm. Patients at recruitment were up to the age of 75 years and were followed for a mean of 10 years. The final mean blood pressure was 144/82 mmHg in the tight control group compared to 154/87 mmHg in the less-tight control group. Over 9 years, patients in the tight control

group showed significant reductions in morbidity and mortality, with (i) a 32% reduction in diabetes-related death, (ii) a 44% reduction in fatal and non-fatal stroke, (iii) a 56% reduction in congestive cardiac failure, and (iv) a 37% reduction in developing microvascular complications. The tightly controlled patients were treated with the β-blocker atenolol or the ACE inhibitor captopril, but the study was not sufficiently powered to determine which agent was superior [100].

In the Hypertension Optimal Treatment Trial [101], a total of 18,790 patients with hypertension were randomized into three groups, the aim being to achieve diastolic pressures less than 90 mmHg, 85 mmHg, and 80 mmHg in each group. The trial included about 1500 people with type 2 diabetes, who were aged up to 80 years. There were significant reductions in cardiovascular morbidity and mortality in the tightest controlled group, with a relative risk reduction of 50% compared to placebo.

Unfortunately, the people enrolled into clinical trials tend to be relatively fit and healthy, with a single specific disease that is the target of the trial, but this does not correlate with many of the elderly people with type 2 diabetes seen in primary care. There is, therefore, a significant question as to the applicability of these trials to many older people with type 2 diabetes in primary care.

26.12 Treatment of dyslipidemia

It can be suggested that there is an evidence base for cholesterol lowering up to the age of about 84 years in people with type 2 diabetes. In the Heart Protection Study (HPS) [102], patients aged up to 80 years were recruited and followed for a mean of 4 years. Treatment with simvastatin (40 mg per day) resulted in a 27% reduction in the incidence of first non-fatal myocardial infarction, and a 25% reduction in first incidence of fatal or non-fatal stroke as compared to placebo. Hence, it could be suggested that there is an evidence base for cholesterol lowering with a statin up to 84 years.

In the CARDS study [103], a total of 2838 people aged 40–75 years with type 2 diabetes and no CHD but who had one other risk factor for CHD (e.g., hypertension or smoker) were randomized to atorvastatin (10 mg per day) or placebo. The trial was stopped 2 years earlier than expected because the pre-specified early stopping rule for efficacy had been met; hence, the median duration of follow-up was 3.9 years. Compared with placebo, the risk reduction in the atorvastatin group for a CHD event was 37%, for stroke 48%, for coronary revascularizations 31%, and for death 27%.

In the FIELD trial [104], 9795 patients aged 50–75 years with type 2 diabetes (2131 with prior cardiovascular disease) received fenofibrate 200 mg daily or placebo. The primary endpoint was initially coronary mortality but was later broadened to include non-fatal myocardial infarction. After 5 years, there was no significant reduction in fatal myocardial infarction or total mortality. There was a 24% reduction in non-fatal myocardial infarction and a 21% reduction in coronary revascularization. Fenofibrate was also associated with a reduction in albuminuria progression and in retinopathy needing laser treatment but there were slight increases in pancreatitis and pulmonary embolism compared to the placebo group.

The European Diabetes Working Party Guidelines for Type 2 Diabetes in older people [29] make the following recommendations about lipid therapy:

1. A statin should be offered as primary prevention if absolute 10-year cardiovascular risk is >15%.
2. A statin should be offered if there is an abnormal lipid profile in the setting of proven cardiovascular disease.
3. Statin therapy should be considered to reduce stroke risk as part of secondary prevention of cardiovascular disease.
4. A fibrate should be considered if triglycerides remain >2.3 mmol/l after at least 6 months statin treatment.

26.13 Aspirin therapy

At this time there is insufficient evidence to recommend routine use of aspirin to older people with diabetes for primary prevention of cardiovascular disease or stroke. However, all patients with type 2 diabetes should be offered aspirin treatment at a dose of 75–325 mg daily for secondary prevention [29].

26.14 Co-morbidities and special circumstances

26.14.1 Cognitive impairment and dementia

Diabetes is associated with an increased risk of dementia and cognitive decline [105–114]. However, many older patients with cognitive decline and dementia are

undiagnosed, particularly in early stages, despite the fact that these conditions have important implications in terms of self-management and concordance with recommended management. It is recommended that at diagnosis and then at regular intervals thereafter, patients over 70 years old should be screened for cognitive impairment using a tool such as the Mini Mental State Examination score [29].

Optimal glycemic management and prevention of repeated hypoglycemia in older patients with diabetes may reduce the risk of developing cognitive impairment or dementia [115, 116].

26.14.2 Depression

Depression is more prevalent in older patients with diabetes compared to those without diabetes [117, 118]. Depression in diabetic patients has not only been associated with poorer glycemic control, less home monitoring of blood glucose, and higher weight but also accelerated rates of CHD [119].

While depression is often undiagnosed and untreated in older people with diabetes [120], primary care practitioners are ideally placed to identify and treat this condition. Early diagnosis and appropriate treatment may lead to better glycemic control [119, 121].

26.14.3 Polypharmacy

It is common for older adults with diabetes to be prescribed multiple medications to control blood glucose, blood pressure, and lipids as well as co-morbidities such as osteoarthritis, gastro-esophageal reflux disease, cardiac failure, chronic obstructive pulmonary disease, and constipation. One recent study found that middle-aged and elderly patients with type 2 diabetes were prescribed a mean of 8.4 different drug compounds per day while those with type 1 diabetes were prescribed a mean of 5.5 different compounds per day [122]. In this study over 97% of the prescriptions corresponded to recommendations in appropriate guidelines.

Adverse reactions to these medications may, at times, exacerbate co-morbidities and adversely affect quality of life and impair a patients' ability to self-manage their diabetes. It is very important that members of the primary care team ensure that medication lists are regularly reviewed and updated as necessary [6, 67].

Older patients are more prone to problems related to their medications because of the higher number they use and because of a decline in cognitive and physical functioning [123]. Polypharmacy in elderly people with diabetes may be associated with adverse effects specific to diabetes, such as hypoglycemia, as well as those associated with poor adherence, increased risk of drug interactions and other serious or common side effects [122,124,125]. Taken together these effects of polypharmacy can significantly worsen quality of life and sometimes lead to disability or premature death [126].

Pharmacists in primary care in a number of countries have been used to perform treatment reviews on patients taking multiple medications. They are sometimes performed in a patient's home. In some countries, such as the UK and Australia, pharmacists may receive financial remuneration for doing this work [30]. Published studies from around the world [30,31,123,127] have shown that such treatment reviews can be helpful and increase the proportion of treatment consistent with recommended guidelines. Common components of a treatment review include:

- a review of the patient's past medication history
- a review of all currently administered medications, both prescribed and over-the-counter
- medication education covering reasons for taking each medication, frequency of administration, and enquiry about any side effects
- a review need for any appropriate monitoring, for example renal function when prescribed ACE inhibitors or vitamin B_{12} levels when prescribed proton pump inhibitors or metformin.

A Dutch study [123] found that when pharmacists and GPs discussed a medication review and drew up a care plan together it led to more changes in pharmacotherapy at review 6 months later than when the results were just provided to the GP in a written report. However, the fact that there were no longer significant differences seen at the 9-month review led to the recommendation that such reviews, in order to be effective, need to be integrated into a routine collaboration between GPs and community pharmacists, occurring at least 6 monthly.

26.15 Falls

Falls are very common in elderly people and are a major contributor to loss of independence. There are many reasons for falls being more common in elderly patients with diabetes, including muscle weakness, loss of vision, peripheral and/or autonomic neuropathy, declining

renal function, co-morbidities such as osteoarthritis, and even hypoglycemia.

Good glycemic control in preventing or delaying progression of some diabetes complications may reduce the risk of falls, but intensive glycemic control, with the increased risk of hypoglycemia that is often associated, can increase the risk of falls. Primary care physicians are ideally placed to identify appropriate glycemic targets for elderly patients to balance the risks associated with poor or too intensive control. A similar judgment is required when setting the appropriate blood pressure target for these patients. The primary care team can often also help in identifying other contributions to a patient's risk of falls and may be able to reduce some of those risks with an appropriate strengthening, balance, and exercise program.

26.16 Frailty

Frailty is more prevalent with increasing age and is associated with a higher risk of falls, functional decline, reduced mobility, recurrent hospitalization, increased likelihood of needing institutional care, and death. Frailty also has a major impact on the risk–benefit balance of many treatment options for diabetes and co-morbidities.

In considering frailty in elderly people with diabetes it can be useful to think of a spectrum of frailty from two extremes:

- Those who have type 2 diabetes as their only significant disease and are otherwise fit, healthy and living independently. Approximately one-third of individuals fall into this group, based on data obtained from a large community study in Wales conducted during the 1990s [128]. For people at or near this end of the spectrum recommended targets for primary prevention, if age-specific evidence is not available, would usually be to consider in consultation with the patient evidence-based targets set for younger patients.
- Those who are frail and elderly and have significant co-morbidities, such as arthritis, high dependency levels or significant dementia. For those elderly patients at or near this end of the spectrum it is often more appropriate to aim for symptomatic control, taking care to avoid hypoglycemia, symptomatic hyperglycemia, and intensive monitoring, always in consultation with the individual and/or their carers.

Different health economies in the developed world are looking at models of care that can reduce hospital admissions of frail elderly patients with multiple chronic conditions, including diabetes, to try to reduce rapidly growing health expenditure. Many of these involve forms of community case management. One such model, based on a system from the USA, uses nurses in a managed-care program called Evercare. In one evaluation study directed specifically at long-stay nursing home residents [129], the provision of a case manager reduced hospital admissions by 50% over a 15-month period compared to controls. The Evercare program has also been tested in the UK using proactive nurse-led assessment and intensive case management in the community rather than in a nursing home setting. One qualitative review of several models being tested in the UK identified many anecdotal stories of unplanned hospital admissions that had been avoided but there was no objective evidence of reduced admissions [130].

One study looked at the rates of emergency admission, emergency bed days, and mortality in nine primary care trusts in the UK, using the Evercare model. A total of 62 Evercare practices were compared to more than 6900 control practices in England. There was no significant benefit in rates of emergency admission, emergency bed days, and mortality in a high-risk elderly population aged over 65 years. The authors concluded that the case management of frail elderly people introduced an additional range of services into primary care, without any associated reduction in hospital admissions [131].

One possible explanation is that case management approaches lead to increased case findings that cancel out the reductions in admissions produced by the model. Similar results were seen in early Australian coordinated care trials [132].

Case management is highly acceptable to the key stakeholders involved, especially to patients, carers, and case managers. Patients and carers report benefits in terms of improved quality of life (better communication and psychosocial support) and reduced GP workload [130]. Other complications have been identified in case management programs. One is the possible conflict between primary and hospital providers, especially when, as in the UK system, hospitals may be paid per case treated, leading potentially to financial incentives to increase admissions that would appear to conflict with the aims of case management [130]. Case management may also paradoxically increase patients' independence by allowing greater capacity for living in their own homes while increasing psychological and practical

dependence on case managers, resulting in reluctance to leave the program, even when health improves.

Clearly there is a need for further study comparing different models of case management that also involve a coordinated approach between primary care and hospital care, and that are able to separately identify benefits for existing high-risk patients and extra patients who might be first identified through the case management model.

26.17 Urinary incontinence

Urinary incontinence in elderly patients with diabetes is often a hidden problem. The risk of urinary incontinence, already common in elderly women, is increased by 50–70% in those with diabetes [133–135]. Incontinence in this group has been associated with psychological stress, social isolation, shame, lack of self-confidence, feelings of depression, and reduced quality of life [134,136–139]. There are a number of factors contributing to this increased risk, including obesity, urinary tract and genital infections, autonomic neuropathy, polyuria, and glycosuria. While some studies have shown a reduction in incontinence with weight loss in obese women [140–142], others have shown a worsening of incontinence with exercise 136, 143. The Diabetes Prevention Program studied people with pre-diabetes looking at the effects of intensive lifestyle intervention compared to metformin and to a control group over a mean period of 2.9 years. The investigators found a significant reduction in incontinence (particularly stress incontinence) in women engaged in the intensive lifestyle arm over the course of the study [144]. A reduction in weight was found to account for most of this beneficial effect. Other studies have shown that even weight loss of only 5–10% in women with urinary incontinence can result in significant improvements in incontinence and it has been suggested that improving incontinence may itself help motivate overweight or obese women to lose weight [140, 142]. Interestingly, in a subset analysis from the Look-AHEAD study, intensive lifestyle intervention was also found to reduce existing and new incontinence in overweight or obese men with type 2 diabetes [145].

Many elderly women with incontinence do not seek medical attention for it. In one Dutch study in 14 general practices 64% of women over 65 years old had not consulted a GP for this problem because they considered it a normal consequence of aging [146]. For this reason, it is important that elderly patients are asked about incontinence rather than assuming that if they had a problem they would raise it with the doctor. Enquiring about the presence of incontinence may be also be important when considering different medications in elderly people with diabetes. For example, SGLT2 inhibitors and diuretics may be less appropriate in the presence of incontinence because of the likelihood of exacerbating the incontinence.

Given the high prevalence of urinary incontinence in elderly women with diabetes and the significant adverse effects this causes on quality of life, primary care teams are ideally placed to identify this problem and provide appropriate advice to affected women. Pelvic floor physiotherapy, bladder training, exercise physiologists, and GPs can all have an important role in this area.

26.18 Concordance with recommended treatment

Lack of patient adherence to recommended treatment is not new. The first recorded example was over 2000 years ago when Hippocrates advised physicians:

> "Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed." [147]

Adherence to recommended management is particularly challenging for patients with type 2 diabetes [148–150]. Pharmaceutical treatment regimens are often complex, involving multiple different medications and additional self-care recommendations, including diet control, regular exercise, self-monitoring of blood glucose, foot care, and attendance at multiple appointments with many different health professionals, which can be a significant burden for many patients. Elderly patients often have additional issues relating to cognitive decline, poor health literacy, increased likelihood of adverse reactions because of polypharmacy, and physical difficulty reading labels or opening medication that can worsen adherence. Poor adherence to recommended diabetes pharmacotherapy has been identified as a significant limitation in effectiveness of diabetes therapeutic strategies 151, 152.

A Scottish review of medication adherence in 2920 patients over at least 12 months defined adherence as at

least 90% of prescribed medication doses being dispensed. Adherence was found to be only 31% in those taking sulfonylurea as monotherapy and 34% in those on metformin monotherapy. Trends to poorer adherence in patients taking more tablets each day and in those with more co-medications were also identified [153].

A recent study found that patients were four times less likely to adhere to prescribed medication for every unit increase in total number of prescribed medication and nine times less likely to adhere if diabetes medication required more than once-daily dosing [154]. Adherence was also three times less likely if patients reported concerns about adverse reactions but was twice as likely if patients had at least one microvascular complication.

A number of reviews have examined the effectiveness of different interventions in improving adherence to prescribed treatments in chronic medical conditions [155–158]. Adherence is increased most consistently with behavioral interventions that reduce dosing demands, involve a multidisciplinary team, provide ongoing monitoring and feedback, and are spread over several sessions. However, there is little evidence that improvements in adherence have led to improved patient outcomes.

A simple strategy can be proposed to try to improve medication adherence in older people with diabetes. (Table 26.1).

Table 26.1 Strategy for improving medication adherence in older people with diabetes.

Explanation	• Careful and simple explanations about: • purpose and importance of each medication • when and how it should be taken
Medication dosing	• Minimize the number of tablets to be taken • Minimize the frequency with which tablets need to be taken • Once-daily tablet treatments and combination preparations are preferable if available
Side effects	• Prescribe with strong focus on using medications with minimal side effects
Labelling	• Ensure instruction labels are understandable to the patient • Ensure packaging is accessible to the patient
Dispensing aids	• Consider pre-filled tablet-dispensing systems: • if normal packaging is difficult or • if forgetting whether tablets have or have not been taken is an issue
Family and/or carers	• Enlist the help of family members or carers to assist with medication taking

26.19 Loneliness and social isolation

Primary care teams are well-placed to recognize and try to address loneliness and social isolation in their elderly patients. Both conditions have been associated with higher rates of depression, sleep disturbances, higher blood pressure, and impaired cognition [159, 160]. Living alone at older age has also been found to be an independent risk for multiple falls, poor diet, and functional impairment [161]. Loneliness is more common with advancing age but rates vary significantly across and within different countries and cultural groups. In one report, 40–50% of those over 80 years of age reported frequent loneliness [162]. While loneliness and social isolation often coexist, loneliness is a subjective experience and social isolation is an objective state of lack of ties with other people [162, 163]. For people with diabetes, there are added implications in choice and safety of medication, concordance with prescribed therapy, and attendance at medical consultations. As a starting point, it is important that primary care team members regularly consider these issues in their elderly patients.

26.20 Nursing home patients

Diabetes in nursing home populations is extremely common, with prevalence rates varying from 5.8% to over 26% depending on the type of facility, age range and gender of residents, and way in which diabetes is diagnosed [164–170]. However, it has been found in one study in the UK that a nursing home population with a diagnosed diabetes prevalence of 12% had another 14.7% diagnosed on blood glucose testing during the study [171].

Treatment priorities when treating frail nursing home residents with diabetes are less about prevention of long-term macrovascular and microvascular

complications and more about maximizing quality of life, preserving autonomy, and avoiding hospitalization [172, 173]. This requires a focus on avoiding acute diabetes complications such as hyperglycemia, hypoglycemia, infection, and dehydration. It also requires a careful consideration of factors such as cognitive impairment, risk of falls, and nutrition status when determining individual management strategies [172, 173]. Optimal care in these situations also requires excellent communication between all members of the primary care team, including nursing home staff and the patient or patient's family, and any agreed treatment targets should be clearly documented in the patient's individual care plan [173].

26.21 Preventive health care in older people: another perspective

Mangin *et al.* have argued that single disease models that may be appropriate for younger people should not be applied to preventive treatments in elderly people [174]. In the PROSPER study of more than 5000 participants aged 70–82 years treated with pravastatin and followed up for an average of 3.2 years, there was no improvement from statin treatment compared to placebo in all-cause mortality, despite a small reduction in cardiovascular mortality [175]. It would appear that cardiovascular mortality and morbidity are replaced by cancer, and so preventive treatments in elderly people may select cause of death, often without the patient's informed consent. Other statin trials largely performed on age cohorts that included many younger patients and that showed clear overall mortality benefits have been used to justify the same approach to preventive care for elderly patients despite a paucity of specific research in this age group. Mangin calls for a more sophisticated model to consider the balance of benefit and harm of preventive treatment in elderly people [174]. Rather than just basing management decisions in elderly patients on absolute risk and death prevention, consideration should also be given to overall life extension and reduction in overall morbidity, taking the duration of treatment into account. Mangin also argues that when considering the risks and benefits of treatment, a broader consideration needs to occur than just looking at the adverse effects of medication [174].

26.22 Conclusions

Older individuals with diabetes experience greater morbidity and mortality than those without diabetes and have higher risks for polypharmacy, cognitive impairment, depression, falls, urinary incontinence, impaired mobility, and persistent pain. Optimally managing these co-morbidities and risks requires a broad range of health practitioner expertise and is ideally suited to a multidisciplinary primary health environment.

The broad goals of diabetes management in older people are not significantly different from those of younger people with diabetes. Safely controlling glycemia and management aimed at reducing the other risk factors for macrovascular and microvascular disease remain paramount. However, particularly in frail elderly people with diabetes, the risk–benefit analysis of various interventions is often far more complicated, requiring good communication between primary care team members and often also with those involved in secondary care. In frail elderly people with diabetes, avoidance of hypoglycemia, hypotension, medication interactions, and worsening of other co-morbidities can often be more important than tight control of individual cardiovascular risk factors.

Issues such as polypharmacy, mental illness, risk of falls, frailty, urinary incontinence, social isolation, and medication adherence all need to be considered as part of the management plan.

New models of care are being evaluated to improve quality of life and life expectancy of elderly people in the community with diabetes. These include 'pay for performance' incentives, different uses of multidisciplinary team members, addressing polypharmacy, and poor adherence to recommended management.

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CHAPTER 27

Inpatient diabetes care and admissions avoidance in older people with diabetes

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KEY MESSAGES

- An annual snapshot audit of UK inpatient diabetes care shows that about one in six hospital beds in England are now occupied by someone with diabetes, largely older people with type 2 diabetes.
- The largest absolute excess hospital admission numbers are in the older age bands, with 69% of excess admissions being in those over 55 years old and 25% in the over 75 s.
- Older patients with type 1 diabetes and dementia are particularly susceptible to diabetic ketoacidosis due to variations in activity, food intake, co-morbidities, and behavioral changes, which makes regular administration of insulin and monitoring of diabetes difficult.
- In older people, the presentation of hyperosmolar hyperglycemia state can be remarkably nebulous, with a poorly defined general deterioration in wellbeing.
- Foot disease remains the most common cause for a diabetes-specific acute hospital admission in the UK.
- Discharge planning should be built into the initial assessment process and should look beyond the inpatient episode of care.

27.1 Introduction

As one national example, the UK National Health Service (NHS) faces a relentless and unsustainable rise in emergency hospital admissions (particularly from within the elderly population) and there is an intense national policy focus on admissions avoidance to acute hospitals. The UK National Diabetes Inpatient Audit (NaDIA) [1], an annual snapshot audit of UK inpatient diabetes care, shows that about one in six hospital beds in England are now occupied by someone with diabetes, largely older people with type 2 diabetes, reflecting the prevalence of type 2 diabetes in the UK (Figure 27.1). We also know from the UK National Diabetes Audit [2] that there are rising numbers of people with type 1 diabetes surviving to old age (Figure 27.1), which will impact on hospital admissions as this group may have particular challenges with glycemic management when other co-morbidities, such as dementia, are present. Treatment choices for the elderly with type 2 diabetes are becoming ever more complex, with co-morbidities playing a significant role in determining the best combination of oral and injectable glucose-lowering therapy for individual patients. This chapter outlines some of the challenges we all face in providing good inpatient diabetes care and preventing diabetes-related admissions. Whilst this chapter is UK focused, we feel it is important to report our experiences as they will have implications for other national healthcare systems.

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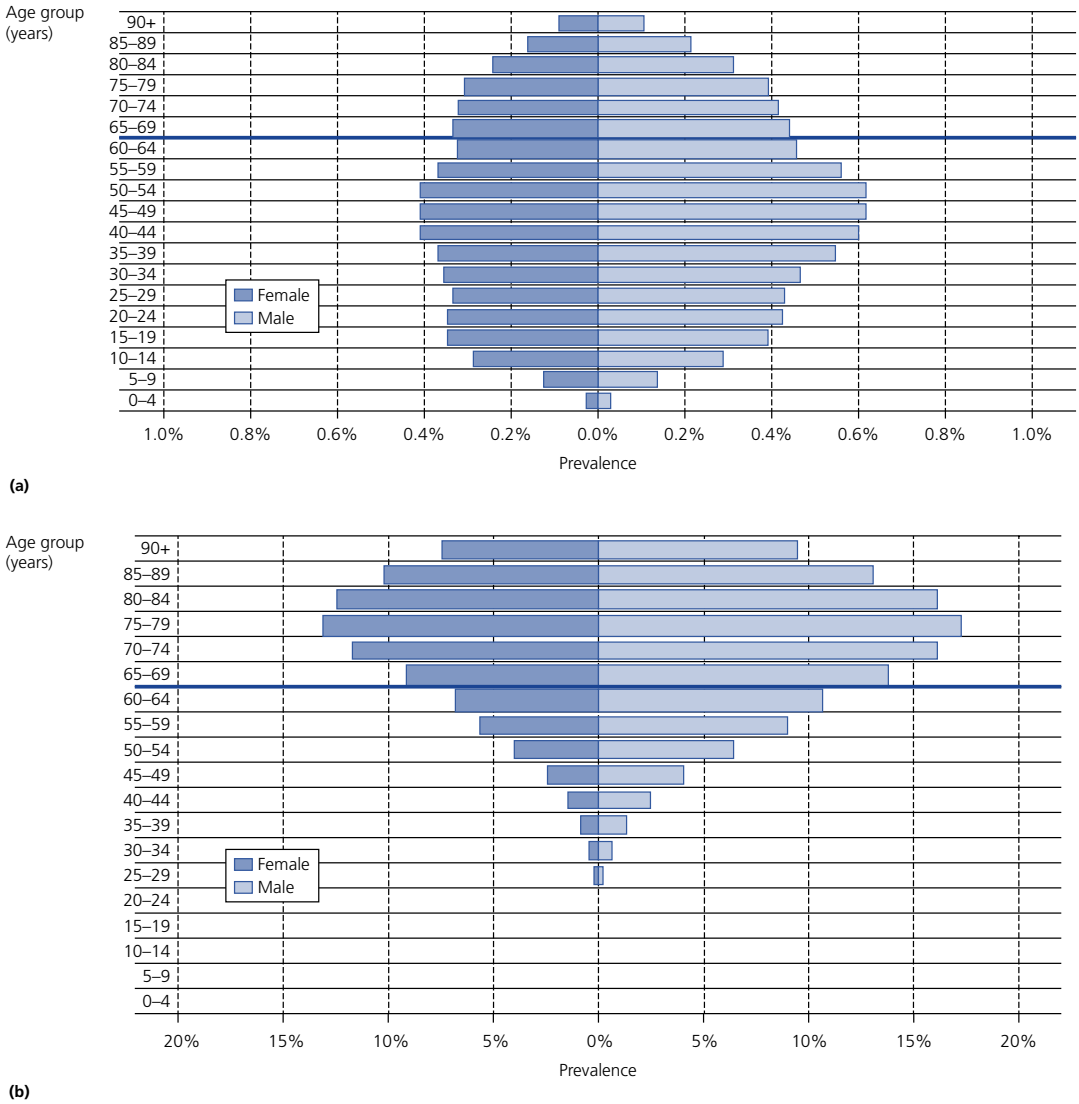

Figure 27.1 National Diabetes Audit 2011–2012 England and Wales, Health and Social Care Information Centre, showing prevalence of (a) type 1 and (b) type 2 diabetes according to age and gender.

Ten per cent of the UK NHS budget is now spent on diabetes, the vast majority on the treatment of complications and prescribing costs, but there are also substantial costs associated with inpatient diabetes care [3]. In 2009–2010 there were over 1 million admissions to hospitals in England and Wales where diabetes was coded [3], but in only a minority of these admissions was there a primary diabetes diagnosis. It is clear that the vast majority of patients are admitted *with* diabetes, rather than *because* of it. The estimated cost of UK hospital admissions (2009–2010) associated with diabetes was £2.3 billion, rising to £2.5 billion if additional co-morbidities are taken into account. Health economic analysis [3] suggested that diabetes admissions in England alone accounted for over 607,000 excess bed days (compared to the equivalent population without diabetes), at a total estimated excess expenditure of £573 million in one year. This is due to

an increase in admission (and readmission) rates, a prolonged length of stay once admitted, a bias against day-case surgery (particularly in the older population), and diabetes-specific admissions for ketoacidosis, hypoglycemia, and diabetic foot ulceration. In addition, there is significant variability in diabetes admission and readmission rates across England, which can only be attributed to variations in standards of care.

Eighty per cent of admissions to hospital associated with the presence of diabetes are emergencies [3]. Whilst the highest relative risk of emergency admission is in the younger age bands (largely those with type 1 diabetes), the largest absolute excess admission numbers are in the older age bands, with 69% of excess admissions being in those over 55 years old and 25% in the over 75s. The presence of two or more long-term conditions predicts a high risk of hospital admission and the use of risk prediction models (e.g. Patients At Risk of Readmission, PARR++) is valuable in managing susceptible patients and coordinating care, focusing on the needs and expectations of the patient and their carers. Health and social care integration in managed disease networks has demonstrated a reduction in emergency admissions for diabetes [4]. The model of clinically-led managed networks for diabetes in England is the recommended approach to practically organize the system of diabetes care to reduce hospital admissions. Its aim should be to deliver high-quality, coordinated care using care pathways and guidelines, and to encourage team-working across different providers to make improvements and monitor outcomes [5]. Creating a practice-based register of older people with diabetes at increased risk of hospitalization is important and should include those aged 80 years and over, residents of care homes, and those with a recent hospital admission, a recent disabling stroke, significant frailty, and increasing cognitive impairment.

27.2 Diabetes admissions from the care home population

Diabetes UK estimate that one in four care home residents have diabetes and that a person with diabetes is admitted to hospital from residential care every 25 min [6]. An early report by the Institute of Diabetes for Older People (IDOP) [7] noted that the median age of inpatients with diabetes in over 200 acute trusts was 75, and that the majority had been admitted as an emergency. Factors which increase the likelihood of hospital admission in the elderly include care home residency, mismanagement of medication, and carer fatigue, amongst others. There are substantial challenges in managing older residents with diabetes in care homes, who form an often forgotten population of people with diabetes who experience poor diabetes care [8]. About 27% of UK residential and nursing home residents have diabetes and there has been little effective implementation of national guidance for improving diabetes care in UK care homes [7] despite evidence that residents with diabetes have high rates of *avoidable* hospital admission and morbidity [7, 8]. There are major UK shortfalls in coordinated foot and eye care for these patients, in training and education of staff in diabetes care, and in the knowledge of care home owners and managers of national guidance on diabetes in care homes. This whole area has been brought into focus (2013) by the National Care Home Diabetes Audit of more than 2000 care homes led by the Institute of Diabetes for Older People (diabetesfrail.org) in 2013, which found that:

- which found that:
  - 35.2% of residents did not know about signs and symptoms of hypoglycemia
  - 36.7% of care homes had no written policy for managing hypoglycemia
  - 63.2% of care homes had no designated staff member with responsibility for diabetes care.

The National Care Home Diabetes Audit therefore identified key areas for action, and six principal audit indicators for care quality, with an emphasis on risk stratification, safety and training, supported by national guidance, and online training and materials for staff.

27.3 Reducing diabetes admissions: A whole-system approach

A whole-system approach to preventing diabetes admissions can show encouraging outcomes with service redesign. Current guidance on commissioning diabetes services highlights the important role diabetes networks play in facilitating integrated working [4], as integrated services have demonstrated reductions in emergency admissions [9]. Structured diabetes clinics in primary

care are also significantly associated with reduced admission rates for diabetes [10]. Community diabetes teams, including primary care services, need to be alert to the special vulnerabilities often present in frail older patients with diabetes, including those living in residential and nursing homes. Educational strategies implemented by these teams should involve families and carers, and include the training of healthcare assistants in care homes.

27.4 Diabetes medication

Older people are more likely to be taking multiple medications, increasing the risk of side effects, medication errors, and hospital admission. In 2010, the Department of Health (DoH) published the Care Homes Use of Medicines Study [11]. It examined medication prescribing, dispensing, administration, and monitoring across 55 care homes in three areas of England. On average, each care home resident was taking eight medicines each. On any one day 7 out of 10 patients experienced at least one medication error. Contributing factors included inaccessible doctors, or doctors who did not know the residents and lacked information in homes when prescribing, the home staff's high workload, lack of medicines training and drug round interruptions, lack of team work among home, practice, and pharmacy, and inefficient ordering systems. This report highlighted the unacceptable prevalence of medication errors in care homes, affecting some of the most vulnerable members of society. This led to the DoH Alert 001 (2010) requesting that primary care trusts (PCTs) plan how medication errors in care homes can be reduced, and in some areas this has resulted in the development of local care homes medicines management services commensurate with all five of the NHS Outcomes Framework Domains [12]. We also know that insulin-treated patients are susceptible to risks associated with its prescribing, dispensing, and administration. Between August 2003 and August 2009 the National Patient Safety Agency (NPSA) received 3881 wrong dose incident reports involving insulin (patient safety alert NPSA/2011/PSA003) the majority caused by getting the wrong insulin products(s), insulin omission or delay, or insulin dose errors. The NPSA issued a rapid response alert (June 2010) on the Safe Use of Insulin is of value in many healthcare environments [13] (Table 27.1).

27.5 Hyperglycemia

27.5.1 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is fortunately rare in the elderly, predominantly affecting young patients with type 1 diabetes [14]. However, elderly patients with type 1 diabetes and dementia are particularly susceptible to DKA due to variations in activity, food intake, co-morbidities, and behavioral changes which makes regular administration of insulin and monitoring

Table 27.1 NPSA recommendations for reducing insulin errors (2010).

For IMMEDIATE ACTION by all organisations in the NHS and independent sector. The deadline for ACTION COMPLETE was 16 December 2010

An executive director, nominated by the chief executive, working with the chief lead pharmacist and relevant medical/nursing staff should ensure that:

1. All regular and single insulin(bolus) doses are measured and administered using an insulin syringe or commercial insulin pen device. Intravenous syringes must never be used for insulin administration.
2. The term 'units' is used in all contexts. Abbreviations, such as 'U' or 'IU', are never used.
3. All clinical areas and community staff treating patients with insulin have adequate supplies of insulin syringes and subcutaneous needles, which staff can obtain at all times.
4. An insulin syringe must always be used to measure and prepare insulin for an intravenous infusion. Insulin infusions are administered in 50 ml intravenous syringes or larger infusion bags. Consideration should be given to the supply and use of ready to administer infusion products, e.g. pre-filled syringes of fast-acting insulin 50 units in 50 ml sodium chloride 0.9%.
5. A training programme should be put in place for all healthcare staff (including medical staff) expected to prescribe, prepare and administer insulin. An e learning programme is available from https://nationalpatientsafetysuite.virtual-college.co.uk/.
6. Policies and procedures for the preparation and administration of insulin and insulin infusions in clinical areas are reviewed to ensure compliance with the above.

of diabetes difficult. The development of near-patient testing of blood ketones has been a significant step forward in detecting metabolic decompensation at an earlier stage than is possible with urine ketone testing, a semi-quantitative method [15–17]. Capillary blood ketone testing is a rapid bedside test and can guide the need for additional rapid-acting insulin administration in conjunction with close monitoring of capillary blood glucose levels. It is also a useful test to determine the patient at risk of DKA and need for rapid hospital admission. Close liaison with the diabetes specialist team by telephone, and the deployment of "sick-day rules" using additional doses of quick-acting insulin, can support elderly patients and their carers in this situation as occasionally this may prevent the need for hospital admission. A major barrier to monitoring of capillary blood glucose (and capillary ketones) in residential homes has been the requirement of district nurses to perform the tests. South Staffordshire Primary Care Trust introduced a project upskilling some care home staff to perform capillary blood glucose monitoring and this, along with continued education and ongoing support, ultimately reduced emergency admission to hospital by 70% (5). Once admitted, there are now national guidelines on the management of DKA [18].

27.5.2 Hyperosmolar hyperglycaemic state

In the elderly, the presentation of hyperosmolar hyperglycaemic state (HHS) can be remarkably nebulous, with a poorly defined general deterioration in wellbeing. The typical HHS history is of several weeks of gradually worsening osmotic symptoms and/or a general deterioration in health. As HHS develops over many days, the dehydration and metabolic disturbances are more extreme than those associated with DKA. The precise prevalence and incidence of HHS is difficult to determine because of the lack of population-based studies and the multiple co-morbidities often found in these patients. The overall prevalence is estimated at less than 1% of all diabetes-related hospital admissions [19, 20]. Incidence of HHS has been estimated at a rate of 17.5 per 100,000 patient-years [21]. Mortality in hyperglycemic crises is primarily due to the underlying precipitating illness and only rarely to the metabolic complications of hyperglycemia or ketoacidosis [22, 23]. The prognosis of hyperglycemic crises is substantially worse at the extremes of age and in the presence of coma and hypotension [19, 20, 23, 24]. Mortality increases significantly above the age of 70 years [20]. The characteristic features of a person with HHS include:

- hypovolaemia
- marked hyperglycemia (30 mmol/l or more) without significant hyperketonemia (<3 mmol/l) or acidosis (pH > 7.3, bicarbonate > 15 mmol/l)
- osmolality usually 320 mosmol/kg or more.

Whilst the reasons why these patients do not become ketoacidotic are not fully understood, hyperglycemia and hyperosmolality are insufficient to make the diagnosis [25]. HHS may be the presenting feature of diabetes in a proportion of cases so there may not necessarily be a past history of diabetes. However, the majority of patients will already be known to have type 2 diabetes. Infection is a common precipitant of HHS; symptoms such as fever, cough, dyspnoea, and dysuria should be sought. There are, however, any number of pathologies leading to increased insulin resistance which can precipitate HHS, including myocardial infarction, stroke or an abdominal catastrophe such as infarcted bowel and so on. Such precipitants require consideration in the unconscious patient who is unable to give a history. In others, the cause is simply a deterioration in glycemic control as part of the natural history of type 2 diabetes, which has led to a worsening osmotic diuresis and progressive dehydration. A drug history is essential, as patients may have pre-existing chronic kidney disease and be taking a number of nephrotoxic drugs, which in addition to the dehydrated state will contribute to the development of acute kidney injury. Metformin in this situation increases the risk of lactic acidosis developing and should be stopped. Some authors [26, 27] have suggested that changes in mental performance correlate with the severity of hyperosmolality, confusion is common with an osmolality greater than 330 mosmol/kg. If patients have been self-blood-glucose monitoring, they may well have recorded a rising blood glucose level in preceding weeks and either not acted on it or received poor-quality medical advice. More commonly, however, the patient is diet- or tablet-treated and not performing blood glucose monitoring, either because there is a perception that this is not needed (particularly if the patient is not prescribed a sulfonylurea or insulin therapy) or there is no facility for the patient to be routinely monitored in a care home setting. An absence of capillary blood glucose data misses this crucial warning sign. Guidance for care home staff on blood glucose monitoring and how to

access this should be routinely available. Nursing home populations are at risk for HHS as co-morbidities that prevent adequate hydration, including immobility, advanced age, debility, dementia, agitation, and restraint use, place these patients at risk. Impaired senses, such as deafness and blindness, may lead to social isolation and also increase the risk of HHS.

The first 24 h or so of treatment are very labor intensive and latest UK guidance recommends that this is undertaken either in a medical intensive care unit or monitored bed in a well-staffed acute admissions ward [28]. The guidance also recommends the use of serial calculations of serum osmolality to monitor response to treatment to avoid over-rapid corrections of the biochemical derangements. HHS is uncommon, but has a higher mortality than DKA [29] and mortality has remained high at 15–20% [30–33]. Rapid shifts in osmolality have been implicated in neurological complications such as central pontine myelinosis, cerebral oedema [34, 35], and death [36].There is also a concern that poor-quality care in these rare HHS patients may contribute to poorer outcomes, with the pitfalls of HHS treatment outlined in recent national HHS guidance [28].Initial treatment is with 0.9% sodium chloride solution alone, and insulin is only introduced when the rate of fall of glucose has plateaued. Controversies persist around the speed and type of fluid replacement [22, 37]. As a general rule of thumb, rapid metabolic changes can be corrected rapidly, but otherwise the correction rate needs to take into account the physiological protective mechanisms induced by the metabolic decompensation. Thrombotic complications, such as myocardial infarction, stroke or peripheral arterial thrombosis, occur more frequently [38, 39], and current guidance [28] recommends the use of prophylactic low-molecular-weight heparin for the duration of admission, with consideration to extending it beyond this in those deemed to be at high risk of venous thromboembolism.

27.5.3 Hypoglycemia

Risk factors for hypoglycemia are highly prevalent in care home residents with diabetes, for example advanced age, multiple co-morbidities, and polypharmacy [40], and these risk factors also carry forward into the acute setting where the NaDIA data suggest high levels of inpatient hypoglycemia exposure [41]. It is common for people with severe acute hypoglycemia to be seen by ambulance crews after an emergency call [5]. Most patients are seen and treated at home, but many are taken to emergency departments and a further proportion are admitted [42]. The available data suggest that there are between 70,000 and 100,000 emergency call-outs per annum in the UK, at significant cost both to the individual and to the NHS. Many of these call-outs might be preventable if appropriate pathways were in place [5]. The National Institute for Health and Care Excellence (NICE) Quality Standard No. 14 states that people with diabetes who have experienced hypoglycemia requiring medical attention should be referred to a specialist diabetes team [43].

Patients in hospital require regular blood glucose monitoring, the frequency of which may vary depending on the type of treatment being used, for example a stable patient on diet or metformin alone may only require once-daily testing, but for another patient on insulin this will need to be increased to four times daily pre-meals and bed to establish a glycaemic pattern. There are many factors which may influence fluctuations in blood glucose levels in elderly inpatients, not least of which are appetite, mobility, the presence of acute kidney injury or hypovolemic states, and cognition. Thus, staff caring for the elderly patient in hospital need to be acutely aware of the need to regularly review blood glucose monitoring results and be prepared to alter therapy in the short term. Diabetes inpatient specialist teams, where available, have been shown to reduce lengths of stay and medication errors [3, 44, 45], and are an extremely valuable resource in supporting patients and staff to optimize diabetes management in hospital.

Hypoglycemia has been shown to be associated with increased mortality, particularly in older patients [46]. Perverse UK incentive payments for tough glycaemic (Quality Outcomes Framework) targets have led to inappropriate HbA1c reduction in many older patients, placing them at risk of hypoglycemia and its consequences; current international recommendations should allow for glycemic targets to be individualized, taking into account co-morbidities and quality of life [47]. All patients on insulin or sulfonylurea treatment should be self-monitoring their blood glucose, or have this monitored if they are unable to do so independently. NHS Diabetes published guidance on the management of hypoglycemia in the community [48], and in addition the Joint British Diabetes Societies Inpatient Group has published guidance on the

management of hypoglycemia in hospital [49], advocating the use of "hypo boxes" containing rapid-acting glucose and long-acting carbohydrate remedies which are quickly obtainable for staff to treat patients.

27.5.4 Diabetes education

A Diabetes UK report on care homes and a further report published on inpatient care [7, 50] repeatedly stated the importance of patient education and, in the case of care homes, education of staff. Improving the care of older people with diabetes in residential care will help to prevent unnecessary admissions, reduce hospital costs, and improve residents' quality of life and experience of care. Structured education for carers as well as patients, where appropriate, covering basic information on diabetes and dietary issues with practical aspects of menu planning, instruction on blood glucose monitoring, and future care planning, with the support of care home managers, will enhance the quality of care in care homes and be commensurate with current national recommendations.

27.5.5 Inpatient care of diabetic foot in the elderly patient

Foot care remains an important part of the management of anybody with diabetes but has particular importance in older people. Foot ulcers tend to occur due to a combination of peripheral neuropathy, peripheral vascular disease (PVD), and excess shear stress. The prevalence of neuropathy and PVD increases as the length of time that somebody has had diabetes increases. Foot disease remains the most common cause for a diabetes-specific acute hospital admission in the UK, with data showing that £1 in every £150 spent in the UK NHS is spent on the care of the diabetic foot [51]. Most of this expenditure has been estimated to be preventable.

Annual foot assessment by an appropriately trained healthcare professional has long been part of the standard of care for people with diabetes and should start at the time of diagnosis for people with diabetes [52]. Foot assessments may need to be carried out more frequently in the elderly because they are more likely to have had diabetes for a longer time, have poor vision, have poor footwear, smoke, be socially deprived or live alone [53]. NICE also recommends that special arrangements should be made "for people who are housebound or living in care or nursing homes to ensure equality of access to foot care assessments and treatments" [53]. Despite these recommendations, it has been shown in the 2013 National Inpatient Diabetes Audit that only 42% of patients had their feet examined during their hospital admission, and that 1.4% of patients developed a foot wound whilst in hospital [54]. Diabetes UK has produced a series of excellent leaflets, which are freely available, to help patients and their carers look after their feet [55].

Prevention of foot disease involves regular assessment of the peripheral circulation and a neurological examination, checking for loss of protective sensation. Established diabetes-related foot disease is also associated with a high amputation rate and increased morbidity and mortality [56]. It has been estimated that between 20% and 40% of people with diabetes have a degree of neuropathy [53]. Whilst there is no consensus as to the best way to diagnose peripheral neuropathy, the practising clinician needs to choose two or three different modalities of sensation to measure and stick to them, so that they become familiar with what is normal and what is abnormal. Commonly used modalities are vibration perception threshold, using either a 128 Hz tuning fork applied to the tip of the big toe and asking the patient to indicate when they feel that the vibration stops or a neurothesiometer, where the value for detecting vibration perception threshold should be less than 25 V. In addition to this, light touch sensation can be assessed using a 10 g monofilament applied to three places on the foot, usually the pulp of the big toe and underneath the first and fifth metatarsal heads. The ability to detect 1 or less applications is indicative of neuropathy. The Ipswich Touch Test is a new method that can be done by anyone at the end of a bed and involves the simple act of lightly touching or resting the tip of the index finger for 1–2 s on the tips of the first, third, and fifth toes and the dorsum of the hallux. This test has excellent correlation for positive and negative predictive values compared with more sophisticated techniques [57].

PVD in patients with diabetes is often distal (femoropopliteal and tibial) [58]. PVD also progresses faster in the diabetes population. The prognosis of patients with a diabetic foot ulcer and PVD is poor, with 50% dying at 5 years or within 2 years following a major amputation [59].

If there is evidence of PVD, with symptoms of intermittent claudication, or the presence of tissue loss due to ischemia or injury, then early involvement of a

vascular surgeon is necessary. In many older patients an aggressive approach to revascularization may not be appropriate and they may not be fit for a bypass operation.

If a foot ulcer is present then a referral to the specialist diabetic foot multidisciplinary team is recommended. In addition to addressing blood supply, the treatment should tackle any infection that may be present by prescribing appropriate antibiotics, if this is necessary [60]. In addition, off-loading the wound – relieving the excess pressure on and around a wound to allow maximal blood flow – will be necessary using wound debridement, appropriate footwear or a specific off-loading device (e.g. a total contact plaster cast or below-knee removable boot).

27.5.6 Perioperative care in the older person with diabetes

People with diabetes are more than twice as likely to be admitted for hospitalization than people without diabetes [61]. There are many reasons for this, but it is partly because older people with diabetes are less likely to be offered day-case surgery, and more likely to have emergency surgery. They also have longer lengths of stay following surgery and a higher rate of 28-day readmissions following surgery [62].

In addition to having diabetes, perioperative diabetes control is also important and poor control has been shown to be related to adverse outcomes in several different surgical specialties. These include (but are not limited to) general surgery [63, 64], cardiac surgery [65], vascular surgery [66, 67], neurosurgery [68], orthopedic surgery [69, 70], colorectal surgery [71], trauma [72], breast surgery [73], liver transplantation [74], hepato-billiary and pancreatic surgery [75], cholecystectomy [76], and foot and ankle surgery [77]. These adverse outcomes include wound infection, length of time in hospital, acute kidney injury, myocardial infarction, time spent on the intensive care unit or on a ventilator, and death.

An analysis of day-case surgery in 2009/2010 showed that the over 75s were the group who were most likely to be denied day-case admission, with approximately 85,500 patients denied day-case surgery during that year, equating to an estimated excess cost of over £25 million [3].

High glucose levels in hospital are associated with harm in middle-aged and older people with diabetes. In a study of over 3100 unselected surgical patients presenting to a single unit in the USA, those people who were known to have diabetes with normal blood glucose levels were at the same risk of developing post-operative morbidity and mortality as those people without diabetes, but if they were known to have diabetes and had high blood glucose levels of up to 16 mmol/l then they were twice as likely to die. However, the risk was greatest in those individuals who were not previously known to have diabetes. If they had pre-operative hyperglycemia then their risk of 30-day mortality was 12 times higher than those people who had normal blood glucose levels. This risk was greatly enhanced if the individual had post-operative hyperglycemia, with a risk of mortality of over 40 times that of somebody with normal blood glucose levels. This compared with the risk of death of only double that in somebody who was previously known to have diabetes. Therefore, having a diagnosis of diabetes was important in helping to prevent post-operative morbidity and mortality [63]. More observational data from over 11,600 patients showed that having hyperglycemia post-operatively was associated with a doubling of the risk of wound infection, an increase in risk of 2.7 of dying, 1.8 times the risk of requiring re-operation, 2.4 times the risk of having an anastomotic failure, and 1.15 times the risk of having a myocardial infarction, compared with a virtual halving of risk of these complications in those people who were known to have either insulin-treated or tablet-treated diabetes [64].

The Joint British Diabetes Society has published guidelines on the peri-operative management of patients undergoing surgery [78], and this documents the patient pathway from primary care responsibilities through to surgical outpatients, the pre-operative assessment clinic, what should happen to the patient during the hospital admission, whilst they are in theatre and recovery, and post-operative care and discharge home.

27.5.7 Discharge from hospital

This is a critical point in the patient journey, which has the potential for great impact if not done well. The DoH recognizes that good discharge planning from hospital back into the community improves patient experience, and reduces length of stay and readmission rates. The DoH's 2010 publication *Ready to go? Planning the Discharge and the Transfer of Patients from Hospital and Intermediate*

Table 27.2 10 key steps to ensure safe and timely discharge.

1 Start planning for discharge or transfer before or on admission.
2 Identify whether the patient has simple or complex discharge and transfer planning needs, involving the patient and carer in your decision.
3 Develop a clinical management plan for every patient within 24 h of admission.
4 Coordinate the discharge or transfer of care process through effective leadership and handover of responsibilities at ward level.
5 Set an expected date of discharge or transfer within 24–48 h of admission, and discuss with the patient and carer.
6 Review the clinical management plan with the patient each day, take any necessary action, and update progress towards the discharge or transfer date.
7 Involve patients and carers so that they can make informed decisions and choices that deliver a personalized care pathway and maximize their independence.
8 Plan discharges and transfers to take place over 7 days to deliver continuity of care for the patient.
9 Use a discharge checklist 24–48 h prior to transfer.
10 Make decisions to discharge and transfer patients each day.

Table 27.3 Potential obstacles to achieving optimal glycemic control in hospital.

Infection
Physiological stress/Illness/trauma
Procedures
Nil by mouth status
Fear of hypoglycemia
Fear of injections
Weight gain
Weight loss
Lack of activity
Changes in mealtimes and meal content
Feeding regimes
Steroid therapy
Mismatch between meals and medications
Diabetes is often a secondary diagnosis
Lack of ownership for diabetes care

Care sets out 10 key steps that need to be followed to ensure safe and timely discharge (Table 27.2). For these steps to be followed, early identification of needs can highlight the call for input from the diabetes specialist team (DST) as well as the proactive coordination of an appropriate discharge plan which is communicated among all relevant healthcare professionals and in any transitions amongst health and social services.

The 2012 NaDIA report showed that only half of those patients who should have been referred to the diabetes inpatient team were actually referred [79]. Readmission rates for people with diabetes are higher than for people without diabetes, not infrequently due to diabetes-related complications that could have been prevented by coordinated discharge planning [80]. Early involvement by the diabetes team in ward discharge planning has been shown not only to reduce length of stay but also to improve patient and carer experience, and reduce readmission rates, a key health indicator [80].

Pre-admission diabetes medications will frequently need to be changed on a temporary or more permanent basis. Examples of this are metformin being stopped due to an acute kidney injury or for contrast radiography, or the initiation of intravenous insulin to cover periods of surgery or fasting. Individuals who have previously been fully independent and self-caring for their diabetes may temporarily or through illness no longer be able to self-manage. Meal timings and eating patterns in hospital will also impact on glucose control and require temporary changes to treatment (Table 27.3).

Discharge planning should be built into the initial assessment process and should look beyond the inpatient episode of care. This proactive approach is aimed at ensuring safety for the patient at home or community facilities, and reducing risk of readmission [81]. Assessment provides the opportunity for information gathering and anticipation of potential problems, which allows for early resolution of barriers to discharge. Clear, sensitive communication with the patient and family is essential, especially for patients who experience a considerable new loss of function [82].

The initial discharge assessment should help to determine which members of the multidisciplinary team will need to be involved during the inpatient stay and in the discharge planning process. Early referral to the DST for involvement in the inpatient care pathway and discharge planning process should include the criteria outlined in the 2011 ThinkGlucose assessment tool

Table 27.4 ThinkGlucose: patient assessment tool and referral criteria.

Always refer	Sometimes refer	Rarely refer
Admission for urgent or major elective surgical procedure	Significant educational need	Minor, self-treated hypoglycemia
Acute coronary syndrome	Intravenous insulin infusion with good glucose control	Transient hyperglycemia
Diabetic ketoacidosis/hyperosmolar hyperglycemic state	Nil by mouth more than 24 h post surgery	Simple educational need
Severe hypoglycemia	Persistent hyperglycemia	Routine dietetic advice
Newly diagnosed type 1 diabetes	Possible type 2 diabetes	Well-controlled diabetes
Newly diagnosed type 2 diabetes	Stress hyperglycemia	Good self-management skills
Intravenous insulin infusion with glucose outside limits	Poor wound healing	Routine diabetes care
Previous problems with diabetes as inpatient	Steroid therapy	
Intravenous insulin infusion for over 48 h		
Impaired consciousness		
Unable to self-manage		
Parental or enteral nutrition		
Foot ulceration		
Sepsis		
Vomiting		
Patient request		

(Table 27.4). These are evidence-based criteria that can facilitate discharge planning and reduce the length of stay.

There is consistent evidence to suggest that best practice in hospital discharge involves multidisciplinary teamwork to actively manage all aspects of the discharge process [83]. The following list of issues should be considered during any discharge assessment:

- normal functional level prior to admission
- physical/self-care limitations, for example blindness, stroke, amputation
- socioeconomic factors, family support
- learning barriers: language, cognition, dexterity, competence related to diabetes self-management
- degree of glycemic control prior to admission
- functional level, ability to self-care
- current diabetes control: treatment, biochemistry
- diabetes management: who administers insulin/tests blood glucose if applicable
- diabetes equipment required: pens, needles, monitoring equipment
- diabetes complications: kidney function, liver disease, retinopathy, neuropathy
- presence of any symptoms
- presence of co-morbidities
- life expectancy, prognosis
- mental capacity: dementia, mental illness
- physical capacity to comply with treatment
- ability to continue/start insulin self-administration
- nutritional status
- educational need: has the diabetes treatment changed, did diabetes lead to the admission?
- educational potential: sight, hearing, manual dexterity, cognitive ability
- mobility
- social support: carers and family circumstances, social services, community support
- dependence on multiagency support for continued care.

The type of discharge may be categorized as simple, complex or rapid (Table 27.5). Elderly patients with complex ongoing health and social care needs, such as frailty, dementia or mental health issues, or requiring a package of care, are considered to have complex discharge needs. Discharge to another care setting, for example a community hospital or nursing home, or of those patients who lack the capacity to make a decision about their long-term care needs will also need particular attention so that the person with diabetes continues to receive coordinated care.

There is considerable potential risk with continuity of medicines management when a patient is moved from one care setting to another [84]. This break in care provision can be avoided by clear lines of communication between the primary and secondary healthcare settings.

Table 27.5 Types of discharge category.

Simple discharge	Complex discharge	Rapid discharge
Involves minimal disturbance to the patient's daily routines Does not prevent or hamper the patient being discharged to their usual place of residence Will not require a significant change in support offered to the patient or their carer	Deviates from the normal discharge pathway and requires complex coordination of services to enable safe discharge May include social work referrals, multidisciplinary meetings, continuing care checklists, and a possible change between admission and discharge destination	May be simple or complex and is usually as a result of the end-of-life pathway or palliative discharge
Example	*Example*	*Example*
Self-caring patient with no decline in functional ability as a result of illness, for example post-operative surgery	Frail elderly patient Patient with a mental illness Patient with learning difficulties Person post limb amputation Person requiring multiagency support Person with dementia or cognitive impairment	Person with terminal illness Transfer to a hospice Transfer to another intermediate care facility

Table 27.6 Roles and responsibilities of hospital staff.

Roles and responsibilities	
Assessment	Ward nurse Diabetes specialist nurse or other member of the diabetes specialist team on receipt of referral
Referral to multidisciplinary team or DST	Ward nurse
Care planning	Patient and/or significant other(s)
Review of discharge plans	Medical team Ward nurse Diabetes specialist nurse Discharge coordinator for complex discharges
Provision of diabetes equipment and literature	Diabetes specialist nurse Ward pharmacist
Ensuring equipment sent on discharge	Ward nurse
Provision of diabetes care plan	Diabetes specialist nurse Ward nurse
Discharge summary	Medical staff Ward nurse
Liaison with GP, district nurse, Community Physician's Network (CPN), carers and care home as appropriate	Diabetes specialist nurse Ward nurse
Follow-up provision clearly documented	Medical team DST

DST, diabetes specialist team; CPN,.

27.5.8 Roles and responsibilities

The roles and responsibilities of staff are important to define to reduce duplication without omitting an important aspect of discharge (Table 27.6).

27.5.9 Discharge coordinators

Early discharge planning may involve a wide range of disciplines which need to be coordinated for a smooth discharge process. Delays in discharge may be due to shortages in resources, poor communication between hospital staff, delays in discharge medication, transport, delays and shortages of specialist staff [85]. Discharge coordinators can often be a single point of contact for the coordination of discharge plans. A model for enhanced discharge planning has been piloted in Worthing and Wolverhampton in the UK, which showed that an integrated approach led to reduced attendance at the emergency department, reduced length of stay, prevention of admissions, pre-assessment support, and reduced cancellations on the day of surgery. Patient safety was not compromised as each person was reviewed within 24 h of admission, enabling early discharge planning and earlier discharges as a result. The model illustrates some of the key characteristics of integrated working as described in by Diabetes UK [86] and NHS Diabetes [87].

27.6 Conclusions

Older people with diabetes occupy a large proportion of hospital beds and are often admitted as a result of non-diabetes-related causes. There are substantial personal and healthcare costs associated with poor inpatient diabetes care, and many diabetes admissions and adverse outcomes in hospital are preventable. This chapter outlines some of these issues and signposts clinicians to the evidence for improvement.

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SECTION D

Management of associated complications

CHAPTER 28
Diabetes and co-morbidities

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KEY MESSAGES

- The terms co-morbidity, multiple co-morbidity, multimorbidity and multiple chronic conditions are used to describe the simultaneous presence of two or more medical conditions in the same patient.
- Co-morbidity is very common in older adults: more than half have three or more chronic conditions, reaching around 70% in adults over 80 years.
- Co-morbidity occurs frequently among older patients with diabetes (not only diabetes-related co-morbidity but also non-diabetes-related co-morbidity) and it is important to highlight this
- Multiple co-morbidities occur in older patients with diabetes, including hypertension, obstructive sleep apnea, fractures, fatty liver disease, urinary tract infections, and hearing loss.
- The best care plan should include the management of all co-morbidities present in an older patient, focusing on maintaining function and a good quality of life.

28.1 Introduction

The terms co-morbidity, multiple co-morbidity, multimorbidity and multiple chronic conditions are used to define the simultaneous presence of two or more medical conditions in the same patient. Co-morbidity is very common in older adults, with more than half of them having three or more chronic conditions, reaching around 70% in adults over 80 years. This greatly increases the complexity of managing diseases and may be associated with poor health outcomes and significant healthcare expenditure. This last statement is controversial, as explained below, in the case of diabetes mellitus.

Many recent studies have paid attention to the issue of diabetes mellitus and co-morbidity. Piette and Kerr [1] were the first to construct a framework to define and study co-morbidity and diabetes mellitus. They divided co-morbidity into three main categories:

- concordant illnesses: those illnesses that overlap with diabetes mellitus in their pathogenesis and management plans
- discordant illnesses: illnesses with unrelated pathogenesis or management plans
- dominant illnesses: illnesses whose severity eclipses all other illness management plans.

This division was made in order to determine the effect of co-morbidity on diabetes mellitus, which should depend on the nature of the co-morbidity: concordant, discordant or dominant. The comparison was made against the recommendations from current guidelines, contrasting whether patients with diabetes received the proper care according to the established recommendations or whether they needed higher levels of care than those in the guidelines. According to Piette and Kerr, patients with diabetes mellitus and concordant illnesses (e.g., hypertension, myocardial infarction, heart failure) received similar or better care for diabetes mellitus than others who did not have these co-morbid conditions. This could be explained by the fact that diabetic patients with other chronic conditions usually are under more rigorous medical control, especially cardiovascular risk factor control, which indirectly improves

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diabetes mellitus control. However, discordant illnesses (chronic obstructive pulmonary disease and osteoarthrosis) may draw resources away from diabetes mellitus because the other conditions usually are more symptomatic and all the care is focused on them, ignoring diabetes mellitus and its possible complications. Finally, dominant illnesses substantially worsened diabetes mellitus care, again according to guideline recommendations, but this assessment, far from being negative, is a positive issue, since the presence of a terminal illness determines the vital prognostic. In this situation, the relief of symptoms due to diabetes mellitus is the only objective [1].

Other studies have shown that services received by old people with diabetes mellitus do not differ based on co-morbid illnesses. In a study where the burden of co-morbid illness was assessed by a commonly used index, the Charlson Comorbidity Index (CCI), no differences in index score were found in the percentage of patients with diabetes mellitus receiving four items of good practice (again according to diabetes mellitus guidelines for patients with diabetes mellitus): HbA1c testing, lipid testing, dilated eye exam and presence of microalbuminuria. Thus there is no evidence about the influence of multimorbidity on the type and level of care received by older adults with diabetes mellitus. Is this finding a signal of the poor care provided to older adults with diabetes? If we were talking about young adults, the answer probably would be yes. This finding should be considered negative for young adults, as it reflects an equally aggressive care/management regardless the burden of disease and, as a consequence, the potential for benefits [2]. As has been clearly established in other chapters of this book, care should be adapted to functional status, not to co-morbid burden. It has been shown that co-morbidity loses its predictive value for both survival and functional decline as age increases. On the contrary, functional status is the best way to categorize older patients in order to optimize care plans and the level of health care. Recent guidelines (IDF Guidelines, ADA/AGS Consensus, EDWPOP) on the management of older people with diabetes mellitus have underlined this. In the context of older people, spending time and effort in classifying co-morbidity or its impact on health care is not as relevant as in younger adults [3]. Nevertheless, co-morbidity occurs frequently among older patients with diabetes (not only diabetes-related co-morbidity but also non-diabetes-related co-morbidity) and it is worth highlighting it. Which are the more prevalent diseases and conditions in these patients (Table 28.1)? According to

Table 28.1 Common conditions present in older people with diabetes.

Condition	Prevalence in older people with diabetes mellitus	Prevalence in older people
OSA	50%	>25%
NAFLD	70% (patients with diabetes mellitus, disregarding age)	10–15% in normal weight individuals (not older people)
Fractures	20% greater risk of any clinical fractures*	Incidence of 517/100000/year (270 men and 695 women)
Lower tract urinary infections	Higher in people with diabetes, including older patients	The prevalence of bacteriuria in patients without an indwelling catheter is 25–50% for women and 15–40% for men The rate of symptomatic infection with fever for both males and females is 0.046–0.126 per 1000 patients-days
Cancer	Slightly higher risk than people without diabetes mellitus but no specific data in older people	The age-adjusted cancer incidence rate is 2151/100,000 population for those over 65 compared to 208/100,000 for those under 65
Hearing impairment	Not significantly higher	74%
Peridontal disease	Higher incidence, prevalence, and severity	70%

OSA, obstructive sleep apnea; NAFLD, non-alcoholic fatty liver disease.
[a] This greater fracture risk occurs despite higher average bone mineral density at the femoral neck in those with diabetes mellitus.

the American Diabetes Association, excluding obesity, hypertension, and dyslipidemia (which are given more attention in other chapters), some of the more common co-morbidities include obstructive sleep apnea, fatty liver disease, cancer, and fractures.

Individuals with diabetes mellitus are also at increased risk of depression, anxiety, and eating disorder diagnoses. This relationship between some mental diseases and diabetes mellitus is bidirectional. Furthermore, mental health co-morbidities of diabetes compromise adherence to treatment and thus increase the risk for serious short- and long-term complications, which can result in blindness, amputations, stroke, cognitive decline, decreased quality of life, and premature death [4].

28.2 Obstructive sleep apnea

28.2.1 Definition

Sleep apnea is a group of chronic sleep-related breathing disorders that are characterized by the occurrence of disordered breathing events during sleep. These events are generally classified into two main types, obstructive and central, depending on whether in the absence of airflow there is ongoing respiratory effort. Obstructive sleep apnea (OSA) is characterized by the predominance of recurrent obstructive events that result from partial or complete collapse of the upper airway during sleep, which is associated with a decrease in oxyhemoglobin saturation and arousal from sleep, and with continued respiratory effort. In contrast, in central sleep apnea the upper airway remains patent, and the apneas and hypopneas result during sleep from a decrease in or lack of respiratory muscle effort.

28.2.2 Epidemiology

OSA is the most common form of sleep-disordered breathing in patients with type 2 diabetes, making up over 80% of cases. Central apnea is significantly less prevalent and is exclusively present in patients with autonomic neuropathy. Because of this distribution in prevalence we will focus on OSA, but it should be noted that these conditions can coexist in the same patient.

Cross-sectional studies of clinic- and population-based samples suggest that up to 50% of patients with OSA have type 2 diabetes, and approximately 50% of patients with type 2 diabetes have moderate-to-severe OSA (Figure 28.1) [5]. Multiple epidemiological studies have shown a bidirectional association between OSA

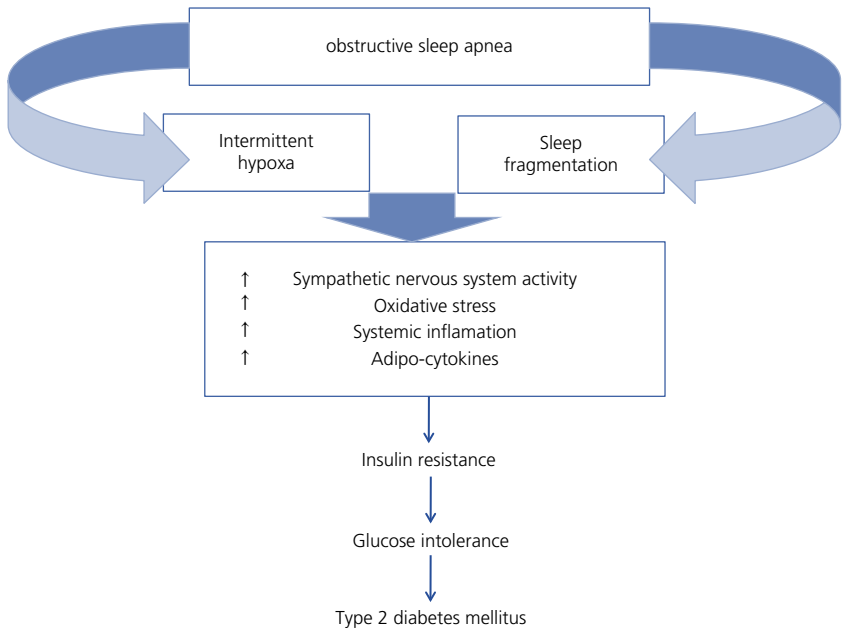

Figure 28.1 Association between obstructive sleep apnea and metabolic abnormalities.

and type 2 diabetes mellitus: recent studies reported an increased rate of OSA among type 2 diabetes community residents even when controlled for obesity and age. At the same time the presence of OSA is an independent risk factor for the emergence of insulin resistance and type 2 diabetes [6].

28.2.3 Pathophysiology

The underlying pathogenetic mechanisms linking OSA and insulin resistance remain poorly understood. Intermittent hypoxia (IH) and sleep fragmentation are the main factors involved in the relationship of insulin resistance and OSA. They affect glucose metabolism in three main ways.

28.2.3.1 Sympathetic nervous system activity

OSA immediately elicits both sympathetic excess of activity and parasympathetic withdrawal. The sympathetic nervous system is activated simultaneously by cycles of apnea-induced hypoxia and CO_2 retention. These cycles produce several effects: stimulation of both central and peripheral chemoreceptors, apnea-induced cessation of pulmonary stretch receptor-mediated inhibition of central sympathetic outflow, and silencing of sympathoinhibitory input from carotid sinus baroreceptors by reduction in stroke volume and blood pressure during obstructive apneas. When the apnea is interrupted by arousal from sleep, the latter process simultaneously augments sympathetic nervous activity and reduces cardiac vagal activity.

28.2.3.2 Hypothalamic–pituitary–adrenal axis

OSA produces alterations in the hypothalamic–pituitary–adrenal axis, generating an increase in corticotropic activity, which leads to an increase in insulin resistance.

28.2.3.3 Effects of intermittent hypoxia

IH is characterized by repeated cycles of hypoxia and reoxygenation. During hypoxia, both cardiomyocytes and neurons produce large amounts of reactive oxygen species (ROS) that contribute to tissue injury and apoptotic cell death. In addition to these cells, pancreatic β-cells are particularly susceptible to oxidative stress damage from the inadequacy of ROS-detoxifying systems.

IH can also activate nuclear transcriptional factors, which stimulates production of inflammatory mediators: cytokines (i.e., interleukin-6), tumor necrosis factor-α (TNF-α) and adipocyte-derived factors (i.e., leptin, adiponectin, and resistin) [6].

Finally, hypoxia has also been reported to increase the tissue levels of long-chain saturated fatty acids. Long-chain saturated fatty acids (i.e., palmitic and stearic acids) can cause loss of secretory function of pancreatic β-cells due to "lipotoxicity." Saturated fatty acids have been shown to induce pancreatic β-cells apoptosis and increase oxidative stress. Furthermore, these effects are magnified under hyperglycemic conditions. However, the synergic effects of IH on the composition of fatty acids in the presence of type 2 diabetes mellitus have not been clearly shown up to now.

28.2.4 Treatment

The effect of continuous positive airway pressure treatment (the specific treatment for OSA) on glucose metabolism is still controversial. Randomized controlled trials are needed to evaluate the ability of OSA treatment to reduce the risk of diabetes and insulin resistance in subjects without diabetes and to ameliorate glucose control in patients with diabetes.

In addition there is a need for further research, using well-designed studies and long-term follow-up, to fully demonstrate a causal role for OSA in the development and severity of type 2 diabetes mellitus. In particular, future studies must carefully consider the confounding effects of central obesity in examining the link between OSA and alterations in glucose metabolism. The interactions among the rising epidemics of obesity, OSA, and type 2 diabetes mellitus are likely to be complex and involve multiple pathways [7]. Finally, the inhibition of ROS generation response to IH can be an important treatment principle to independently restore the normal functioning of the pancreas and control the progression of insulin resistance-induced type 2 diabetes.

28.3 Fatty liver disease

28.3.1 Definition

Non-alcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (e.g., heavy alcohol consumption) are present.

28.3.2 Epidemiology

NAFLD is seen worldwide and is the most common liver disorder in Western industrialized countries, where the major risk factors for NAFLD (central obesity, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome) are common. The prevalence of NAFLD in patients with type 2 diabetes mellitus is approximately 70% [8].

28.3.3 Pathogenesis

The pathogenesis of NAFLD has not been fully elucidated. The most widely supported theory implicates insulin resistance as the key mechanism leading to hepatic steatosis. Obesity and type 2 diabetes, conditions associated with peripheral insulin resistance, are frequently observed in patients with NAFLD, but insulin resistance has also been observed in patients with NAFLD who are not obese and those who have normal glucose tolerance.

28.3.4 Genetic basis for insulin resistance associated with NAFLD

One report found an association with certain polymorphisms in the gene encoding for apoliprotein C3, while another study demonstrated that IL-6 polymorphisms are associated with NAFLD and markers of insulin resistance and inflammation. A third report found polymorphisms in a gene encoding for protein expressed in adipose tissue (adiponutrin) and involved in triglyceride metabolism. Certain variants of the gene were strongly associated with the histologic severity of NAFLD. In addition, alterations in the transcriptional activity of the peroxisome proliferator-activated receptor γ coactivator 1α (PPARGC1A) promoter correlated with the insulin resistance phenotype and the presence of NAFLD. Finally, a single nucleotide polymorphism in the peroxisome proliferator-activated receptor-gamma coactivator 1-alpha gene (PPARGC1A) has been associated with an increased risk for developing NAFLD.

28.3.5 Visceral fat and NAFLD

All the above alterations lead to increased visceral adipose tissue and intrahepatic fat, which is correlated with increased gluconeogenesis, increased free fatty acid levels, and insulin resistance. Visceral fat has also been associated with liver inflammation and fibrosis in patients with NAFLD independently of insulin resistance, an effect possibly mediated by interleukin-6 (a pro-inflammatory cytokine). Several other cytokines and adipokines involved in insulin receptor signaling appear to be altered in omental adipose tissue of NAFLD patients.

The molecular pathways leading to insulin resistance are complex and have not been completely elucidated. Several molecules appear to be involved in interfering with the actions of insulin on a cellular level.

28.3.6 Treatment

Observations from pilot studies have demonstrated the beneficial effects of insulin-sensitizing medications in patients with NAFLD.

28.3.6.1 Metformin

Metformin belongs to a class of insulin-sensitizer drugs and acts through reducing hepatic glucose output, increasing insulin-stimulated glucose uptake in peripheral tissue, and stimulating fatty acid oxidation in adipose tissue. Adenosine monophosphate-activated protein kinase is the main player in mediating metformin effects.

Animal studies have demonstrated that metformin reverses aminotransferase abnormalities, steatosis, and inflammation in mouse models of NAFLD. During the last decade, many clinical trials have evaluated the useful effects of metformin on patients with NAFLD (Table 28.2).

Only a few of these studies were randomized and the results are conflicting. Summing up the main results of these trials, it must be said that metformin improves insulin sensitivity, serum alanine aminotransferase (ALT), and aspartate transaminase levels in the majority of subjects, but it has no significant effect on liver histology. The precise dose and duration of treatment is unknown and the beneficial effects on serum ALT only continue during treatment and were not observed after the disruption of the drug. Metformin does not seem to increase the risk of lactic acidosis and, unlike the thiazolidinediones, it is not encumbered by weight gain or potential hepatotoxicity. According to current data, although it cannot be suggested for the specific treatment of NAFLD or nonalcoholic steatohepatitis (NASH), metformin can be a first-line drug in patients with both NAFLD/NASH and type 2 diabetes mellitus.

28.3.6.2 Thiazolidinediones

Thiazolidinediones (TZDs) are a class of oral anti-diabetic drugs that induce a nuclear transcription factor, peroxisome proliferator activated receptor-γ (PPAR-γ),

Table 28.2 Summary of metformin trials in adult patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

Reference	Study type	Subject number	Therapy	Compared with	Duration	NAFLD vs NASH	Liver enzymes	Histology
Marchesini *et al.* [1]	Open label, single arm	20	Metformin	Baseline	4 months	NASH	Improved	Not assessed
Nair *et al.* [2]	Open label, Single arm	15	Metformin	Baseline	48 weeks	NAFLD	Transiently improved	Mildly improved
Uygun *et al.* [3]	Open label, RCT	36	Metformin	Diet/Exercise	6 months	NASH	Improved	Not improved
Bugianesi *et al.* [4]	Open label, RCT	110	Metformin	Vitamin E/diet	12 months	NAFLD	Improved	Improved
Duseja *et al.* [5]	Open label, RCT	50	Metformin	Diet	6 months	NAFLD	Improved	Not assessed
de Oliveira *et al.* [6]	Open label, single arm	20	Metformin and NAC	Baseline	12 months	NASH	Improved	Improved
Loomba *et al.* [7]	Open label, single arm	28	Metformin	Baseline	48 weeks	NASH	Improved	Improved
Haukeland *et al.* [8]	Open label, RCT	48	Metformin	Diet/Exercise	6 months	NAFLD	Improved	Not improved
Garinis *et al.* [9]	Open label, RCT	50	Metformin	Diet	6 months	NAFLD	Improved	Not assessed
Shargorodsky *et al.* [10]	Open label, RCT	63	Metformin	Placebo	12 months	NAFLD	Not improved	Not assessed

NAFLD, non-alcoholic fatty liver.

by binding selective ligands. PPAR-γ is predominantly expressed in adipose tissue and leads to decreased hepatic fat content and an improvement in glycemic control by increasing insulin sensitivity. TZDs also increase plasma adiponectin levels, activate AMP-activated protein kinase, and induce fatty acid stimulation [9].

Although the results of studies suggest some benefits from TZDs, a major problem also emerges: safety of long-term therapy and adverse effects. The use of rosiglitazone has been highly restricted in the USA and prohibited in Europe due to the increased risk of coronary events. On the other hand, pioglitazone is associated with adverse events such as bladder cancer, bone loss, weight gain, painful swollen legs, and congestive heart failure. After evaluation of the overall results, it would be a good choice to use TZDs for the treatment of NAFLD only in patients with type 2 diabetes mellitus who are also candidates for treatment with a TZD. The American Association for the Study of Liver Diseases (AASLD) guideline recommends that pioglitazone can only be used to treat patients with biopsy-proven NASH, but it also raises a concern about its long-term safety and efficacy in patients with NASH. The guideline also stresses that most of the clinical studies were done in non-diabetic patients and thus the effect of TZDs on NASH of diabetic patients was not established. The position statement of a special European Association for the Study of the Liver (EASL) conference recommends that pharmacological therapy of NASH could be a 1–2 year course of therapy with glitazone [10].

All of these facts make the TZDs a group of drugs with quite limited usefulness in older adults with diabetes mellitus and NAFLD/NASH.

28.3.6.3 Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a new class of drugs and include sitagliptin, vildagliptin, linagliptin, and saxagliptin. DPP-4 is a membrane-associated peptidase with a widespread organ distribution that deactivates a variety of bioactive peptides, such as glucagon-like peptide-1 (GLP-1). Inactivation of GLP-1 causes glucose intolerance, diabetes mellitus, and hepatic steatosis. In a study including 31 NASH patients, Balaban *et al.* reported that serum DPP4 levels were higher in patients with NAFLD compared to controls. Furthermore, the serum DPP4 activity and staining intensity in liver were correlated with a histopathological grade of NASH and hepatosteatosis [11]. In rat models, DPP-4 inhibitors improve hepatic steatosis by increasing insulin sensitivity and decreasing hepatic triglyceride levels. To date, there is no published controlled trial with these agents in humans.

28.3.6.4 GLP-1 analogues

GLP-1, a hormone excreted by intestinal L cells, regulates blood glucose by stimulation of glucose-dependent insulin release. GLP-1 has a direct effect on hepatocytes by inducing the genes responsible for fatty acid oxidation and insulin sensitivity. Ding *et al.* demonstrated that exenatide (a GLP-1 analog) improves insulin sensitivity and reduces hepatosteatosis in rats with fatty liver [12]. A recent meta-analysis including 4442 patients indicated that the GLP-1 analog liraglutide decreased aminotransferase levels and that this effect was dose-dependent. However, controlled studies are needed to show the efficacy of GLP-1 analogs in NAFLD and NASH treatment [13].

28.4 Cancer

Type 2 diabetes mellitus has been associated with an increased risk of liver, pancreatic, colorectal, breast, and bladder cancer in published studies. It has been hypothesized that this link may be due to shared risk factors between the diseases, including obesity, age, and physical inactivity. However, other studies have shown a modest increase in total risk of cancer (HR 1.11–1.78), not only the cancer mentioned above, which raises the possibility that diabetes mellitus is an independent risk factor for cancer. The risk is mostly shown in the youngest age group, supporting the hypothesis that hyperinsulinemia, predominant in the early years of type 2 diabetes mellitus, plays an important role in cancer development.

Limited studies in the past have explored the links between diabetes mellitus and other less frequent cancers, such as head and neck cancer, thyroid cancer, urogenital cancer, endometrial cancer, breast cancer, and non-melanoma skin cancer, and showed that all of them have a slightly higher incidence in people with diabetes mellitus than in those without diabetes mellitus. Age and sex stratification analysis revealed that the risk of cancer increases with age.

However, the causes for such an increased risk need to be fully understood. As mentioned above, shared risk factors, such as obesity, aging, diet, and physical activity, may be associated with the increased risk of cancer [14].

28.5 Fractures

Numerous studies have shown that overall fracture risk is significantly higher for both men and women (although is higher in women) who have type 2 diabetes mellitus than in older people without diabetes mellitus. There are some possible molecular mechanisms through which diabetes mellitus may induce osteoporosis and bone fractures, but these mechanisms are complex and include changes not only in bone but also in muscle tissues. Indeed, diabetes mellitus has a broad spectrum of effects on bone (Figure 28.2):

- It mainly regulates the bone cells (specifically osteoblast and osteoclast) and the muscles, facilitating osteoporosis as well as reduction of muscle strength.
- It negatively influences the normal functioning of osteoblast but positively regulates the osteoclast functioning (facilitating the process of osteoporosis).
- It reduces the availability of mesenchymal stem cell (MSC) to produce osteoblast but simultaneously increases the availability of MSC for adipocyte formation in bone marrow, making the bone fragile and decreasing bone microcirculation, although the average BMD in older patients with diabetes mellitus has been shown to be higher than in older people without diabetes mellitus.
- Diabetic neuropathy also acts as a prominent factor in osteoporosis and muscle atrophy.
- Diabetes mellitus induces vitamin D deficiency, which is an essential factor of bone and muscle activities because deficiency of vitamin D stimulates the production of parathyroid hormone (PTH), which is a negative regulator of osteoblast functioning but a positive regulator of osteoclast functioning. It also causes the reduction of muscle strength because it lowers the rate of Ca^{2+} absorption by the intestine and thereby reduces muscle activity, increasing the rate of falls.

In addition to poor bone quality, diabetes also increases the risk of falls, the main mechanism related to bone fractures in older adults. This increased risk of falls is due to several factors:

- visual problems secondary to the presence of diabetic retinopathy
- abnormal walk caused by polyneuropathy
- heart failure caused by diabetic cardiovascular complications
- poor muscular function, which produces weakness and poor physical performance.

The effect of diabetes mellitus on muscle deserves some consideration. Muscle atrophy is a pathophysiological condition linking diabetes and the risk of fractures that is associated with the depression of protein synthesis and an increase in protein degradation.

Diabetes mellitus is directly associated with muscle atrophy through the increased activity of the ubiquitin proteosome system (UPS), although other pathways may be involved in this process. Inducers of UPS include glucose, TNF-α, Ang-II, glucocorticoid, and IL-6. Most of these exert their effects on myogenesis-responsive genes through an NF-κB mediated pathway. Insulin and vitamin D also exert some role in the mechanisms, leading to muscle weakness in older adults with diabetes mellitus.

High extracellular glucose concentration is a potential precursor of advanced glycosylation end product (AGE) formation. Evidence has shown that AGE may induce the formation of ROS by activating the transcription factor NF-κB. Additionally NF-κB induces the transcription of inducible nitric oxide synthase (iNOS) as well as transcribing the gene MuRF-1, which is responsible for muscle wasting. Furthermore, AGE activates eIF2α, which depresses protein synthesis by decreasing translational efficiency.

NF-κB is also a target for TNF-α. Several studies have indicated that TNF-α is a prominent cytokine in cachexia-induced muscle atrophy as well as a potent inducer of insulin resistance. Binding of TNF-α with its receptor expressed on myocyte activates nuclear transcription factor NF-κB.

Ang-II is the major peptide of the renin-angiotensin system implicated as a modulator of muscle wasting. Ang-II exerts its effect on muscle atrophy not only through the generation of ROS but also through the activation of glucocorticoid and IL-6 as well as through disrupting insulin signaling in muscle cells.

Insulin resistance has been implicated as a potential inducer of overall protein degradation through a mechanism that involves caspase-3 mediated actin cleavage. Finally, beyond its role in osteolysis, vitamin D exerts a

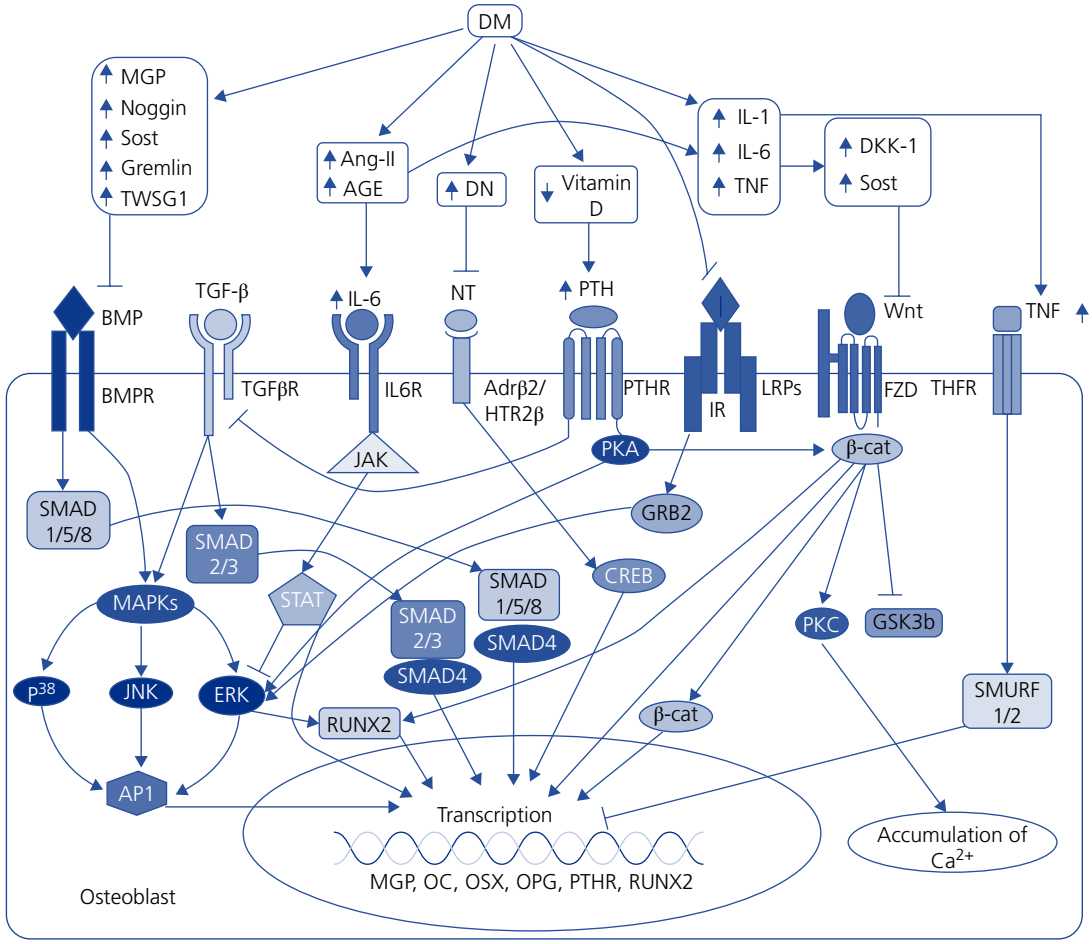

Figure 28.2 Diabetes and osteoblastic activity. BMP, bone morphogenetic protein; TGF-β, transforming growth factor β; BMPR, bone morphogenetic protein receptor; IL-6, interleukin 6; IL-1, interleukin-1; IL6R, receptor IL-6 receptor; PTH, parathyroid hormone; PTHR, PTH receptor; TNT, neurotransmitter; HTR2β, 5-hydroxytryptamine receptor 2 β; I, insulin; IR, insulin receptor; LRP, low-density lipoprotein receptor related protein; FZD, frizzled; TNF, tumor necrosis factor; TNFR, TNF receptor; JAK: janus kinase; STAT, signal transducers and activators of transcription; AP-1, activator protein 1; ERK, extracellular signal regulated kinase; MAPK, mitogen activated protein kinase; RUNX2, runt related transcription factor 2; PKA, protein kinase A; PKA, protein kinase C; β-cat, β catenin; GSK3b, glycogen synthase kinase 3b; SMURF, SMAD ubiquitylation regulatory factor; MGP, matrix gla protein; OC, osteocalcin; OSX, osterix; OPG, osteoprotegerin; DKK-1, Dickkopf related protein 1; Sost, sclerostin; TWSG1, twisted gremlin; Ang-II: angiotensin-II; AGE, advance glycation end product; GRB2, growth factor receptor bound protein.

range of effects in skeletal muscle cells. Muscle activity is a Ca^{2+}-dependent process and therefore is very sensitive to changes in Ca^{2+} levels. A lack of vitamin D can reduce the availability of calcium and phosphorus, and thereby delays muscle activity. Some *in vitro* and *in vivo* trials have shown that vitamin D levels are significantly lower in patients with diabetes mellitus (Figure 28.3) [15].

28.6 Type 2 diabetes and the lower urinary tract

28.6.1 Definition

Different entities are embraced under the topic of diabetes mellitus and the urinary tract: lower urinary tract symptoms (LUTS), asymptomatic bacteriuria (ASB), and urinary tract infections (UTIs).

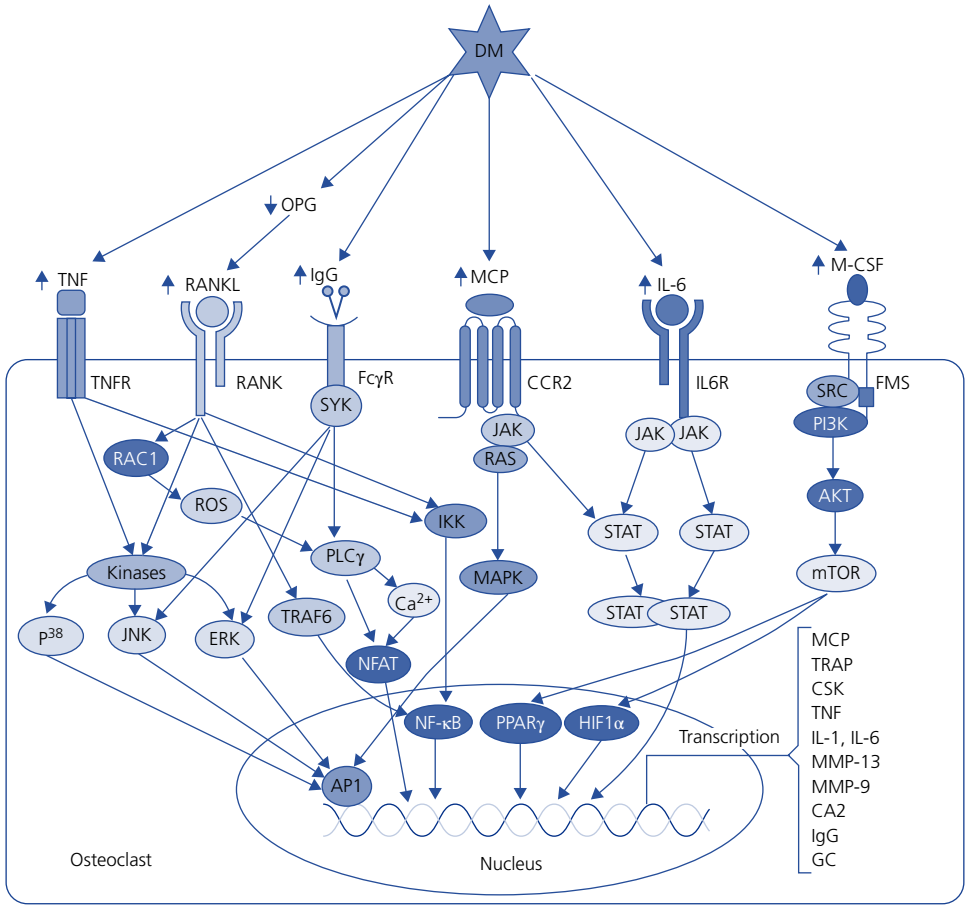

Figure 28.3 Diabetes and osteoclastic activity. MCP, monocyte chemoattractant protein; IgG, immunoglobulin G; NFAT, nuclear factor of activated T cells; ROS, reactive oxygen species; PLCγ, phospholipase Cγ; M-CSF, macrophage colony stimulating factor; PPARγ, activates transcription factors peroxisome proliferator activated receptor γ; HIF1α, hypoxia inducible factor 1 α; FcγR, Fc receptor γ; IL-6, interleukin 6; CCR2, CC chemokine receptor 2; mTOR, mammalian target of rapamycin; OPG, osteoprotegerin; ERK, extracellular signal regulated kinase; JNK, JUN N terminal kinase; TRAP, tartrate-resistant acid phosphatase; CSK, cathepsin K; MMP, matrix metalloproteinase; CA2, carbonic anhydrase 2; GC, glucocorticoid.

28.6.2 Epidemiology

The prevalence of ASB was 29% in women (mean age 59.4 ± 11.4) with type 2 diabetes. Risk factors for ASB in type 2 diabetic women included age, macroalbuminuria, a lower body mass index, and a UTI during the previous year. No association is evident between current HbA1c level and the presence of ASB [16]. Moreover, women with type 2 diabetes mellitus and ASB had an increased risk of developing a symptomatic UTI compared with those without ASB [17]. Results are also now available about (LUTS) in people with type 2 diabetes. The California Men's Health Study showed that people with type 2 diabetes are at high risk for prevalent LUTS (OR = 1.32; CI 95% 1.26–1.38).

Patients with diabetes mellitus have also a higher prevalence of ASB and incidence of UTIs compared with patients without diabetes mellitus. They also more often have bacteremia, with the urinary tract as the most common focus for these infections, as well as a higher mortality outside the hospital compared with patients without diabetes mellitus.

28.6.3 Potential explanatory factors

The increased prevalence of ASB in diabetic women is not the result of a difference in causative bacteria, as bacteria isolated from the urine of diabetic women with ASB showed the same virulence factors and resistance to antimicrobials (particularly for *Escherichia coli*) compared with those isolated from non-diabetic controls. Although bacterial growth *in vitro* is increased after the addition of glucose, glucosuria is not a risk factor for ASB or for the development of UTIs *in vivo*. No differences in granulocyte function tests were demonstrated among diabetic women with ASB, non-bacteriuric women, and healthy control subjects. In contrast, women with both ASB and diabetes mellitus had lower urinary cytokine and leukocyte concentrations than women with ASB without diabetes mellitus. Finally, it has been found that *E. coli* expressing type 1 fimbriae adhere better to uroepithelial cells of women with diabetes mellitus compared with those isolated from women without diabetes mellitus.

28.6.4 Treatment

As the causative bacterium is the same in older people with and without diabetes, the main question to answer is what is the most appropriate duration of treatment for UTIs in diabetic patients? There are no randomized trials that answer this question, but it has been recommended to consider these patients as having a complicated UTI and therefore to treat them for a period of 7–14 days [18].

Diabetes has also been associated with significantly increased risks for cognitive decline, cognitive impairment, and all-cause dementia. The effects of hyperglycemia and insulin on the brain are areas of intense research interest and are discussed elsewhere in this book (Chapter 15).

28.7 Hearing impairment

28.7.1 Epidemiology

Hearing impairment (HI) is quite common in older people. In a population-based cohort study using audiometric threshold testing, the 10-year cumulative incidence of HI was 22% in people aged 48–59 at baseline and 74% in adults aged 70–79 [19].

Although diabetes mellitus and glycemia have been linked with prevalent hearing loss in cross-sectional studies, no longitudinal studies have found a prospective association The Nurses' Health Study found that diabetes mellitus was associated with a slightly, but not statistically significant, greater risk of HI (HR 1.26, 95% CI 0.93–1.71). However, HbA1c appeared to be associated with risk of HI but only at very high or near-normal levels. HbA1c levels ≥12.1% were associated with twice the risk of HI (HR 2.19, 95% CI 1.08–4.61), but this association was not observed for HbA1c levels of 10.1–12% (HR 0.98, 95% CI 0.48–2.01) or 8.1–10% (HR 1.36, 95% CI 0.84–2.19). A modest excess of risk was detected for high normal levels of HbA1c (6.1–8%) with HR 1.21 (95% CI 1.01–1.44). Thus while the diagnosis of diabetes mellitus was not significantly associated with HI, some levels of HbA1c are, suggesting some kind of association between these entities.

28.7.2 Potential pathophysiological links between diabetes and hearing loss

Aging implies many changes to the auditory system. Added to the aging process diabetes mellitus may affect the auditory system through mechanisms similar to those hypothesized for other cardiovascular risk factors: oxidative stress, inflammation, and vascular insufficiency. Traditionally, hyperglycemia has been associated with cochlear changes, including basement membrane thickening in the stria vascularis and basilar membrane. In the National Health and Nutrition Examination Survey there was a suggestion that neuropathy and microvascular factors may be involved in the association between diabetes mellitus and HI.

28.8 Periodontal disease

28.8.1 Definition

Periodontal disease is the destruction of the tissues that support the tooth by accumulation and maturation of oral bacteria on teeth and includes two major entities, gingivitis and periodontitis. Gingivitis is characterized by reversible inflammation of periodontal tissues whereas periodontitis also presents destruction of tooth-supporting structures and may lead to tooth loss. Existing evidence indicates that gingival inflammation (gingivitis) is required for periodontitis although some gingivitis never transforms to periodontitis.

28.8.2 Epidemiology

Periodontal disease has a higher incidence in diabetic patients, and it is more prevalent and severe compared with a healthy population. The risk of periodontitis is three times higher among diabetic patients, with its prevalence and severity even greater in diabetic patients presenting with elevated HbA1c levels [20].

Longitudinal studies have demonstrated that these associations are a two-way relationship between diabetes and periodontitis: periodontal tissue destruction is more severe in diabetic patients and glycemic control is poorer in diabetic subjects with periodontal disease.

28.8.3 Pathophysiology

Several studies have shown how gingival inflammation can be modulated by a number of conditions, especially various systemic diseases such as cardiovascular disorders, respiratory diseases, osteoporosis, immunodeficiencies, and diabetes mellitus.

Furthermore, xerostomia is a frequent symptom found in diabetic patients on oral hypoglycemic agents, a finding that it is also more frequent in older adults, facilitating the onset of some fungal opportunistic infection. Lim *et al.* [21] have consistently found that glycemic control is the most important risk factor related to the severity and extent of periodontitis, establishing that the rate of periodontal destruction is related to inappropriate glycemic control.

Different hypotheses have been proposed to explain the relationship between diabetes mellitus and periodontitis. There is a pathogenic pathway that may justify the biologic plausibility.

A direct causal relationship in which, through the effects of AGEs, diabetes triggers an inflammatory phenotype in cells. Several studies have shown how chronic hyperglycemia produces AGEs that can bind to specific receptors (receptors of advanced glycosylation end products, RAGE) on different cells such as fibroblasts, endothelial cells, and macrophages [22]. Macrophages are thus transformed into hyper-reactive cells that produce pro-inflammatory cytokines such as interleukins 1β and 6 (IL-1β, IL-6) and TNF-α. AGEs can also alter endothelial cells that will become hyperpermeable and hyperexpressive for adhesion molecules, while fibroblasts will show decreased collagen production. AGEs produced by chronic hyperglycemia can therefore produce hyperinflammatory responses, vascular modifications, altered healing, and increased predisposition to infections, providing an appropriate milieu for the development and perpetuation of periodontal disease.

28.8.4 Treatment

Periodontal treatment has been shown to be successful in patients with diabetes. The short-term effects of periodontal treatment are similar in diabetic patients and the non-diabetic population [23], although more recurrence of periodontal disease can be expected in those with poorly controlled diabetes. The beneficial effects of periodontal treatment on HbA1c levels seem to be observed more frequently in type 2 diabetics and when antibiotics are associated with local periodontal therapy. The benefits are modest (HbA1c reduction after periodontal treatment is usually less than 0.5%) and are not present in all the studies. Thus, new studies are needed to evaluate the clinical significance of the HbA1c reduction, if any, taking into account that improvements in the control of both diabetes and periodontal disease have the potential to significantly increase the quality of life in older people with diabetes [24].

28.9 Conclusion

Co-morbidity is a very frequent finding in older adults with diabetes mellitus, but its impact on the prognosis and management of patients is not well understood. It is important to understand the impact of this co-morbidity on functioning and thus design the most appropriate care plan, which should include the management of all co-morbidities present in the older patient, focusing on maintaining function and a good quality of life.

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CHAPTER 29
Diabetes and cognitive dysfunction

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KEY MESSAGES

- Diabetes mellitus and cognitive dysfunction are interrelated, and often coexist in the same individual.
- There is an increasing evidence base linking a greater likelihood of cognitive dysfunction in subjects with diabetes, especially of long duration.
- The assessment of cognitive function using standard cognitive screening tests is recommended in the routine assessment of all older people with diabetes.
- The detection of cognitive dysfunction may provide an early opportunity to consider drug-based intervention strategies and care packages that provide more effective management, and may delay the need for early dependency.

29.1 Introduction

Older patients with diabetes (either type 1 or 2) have an increased risk of developing cognitive dysfunction by virtue of their increasing age, irrespective of other factors such as diabetes itself. Practicing clinicians must expect to see patients with both diabetes and cognitive dysfunction, as both conditions are highly prevalent chronic disease states in our aging societies. The development of dysfunction may have several important consequences for the patient and his/her family and carers in terms of the complexity of care, adherence to therapy, ability to self-manage, and the need for assisted care.

There is still uncertainty about how important it is to screen patients with diabetes for evidence of cognitive impairment and this question is one of four open ongoing controversies in the clinical care of older people with diabetes:

- improving glucose control with active treatment will reduce cardiovascular risk *jury still out*
- early detection of disability may prevent/delay further functional deterioration, for example mobility, ADL function, and falls rate *jury still out*
- there are measurable benefits for actively screening for the presence of cognitive impairment and/or depression *jury still out*
- early detection of diabetes in care home settings may improve well-being, reduce complication rate, and delay onset of further disability *jury still out*

Many of the important elements that have provided a background to the concerns relating to the area of diabetes and cognitive impairment are listed in Table 29.1. Several important lines of work now provide strong evidence that diabetes accelerates the progression of mild cognitive impairment (MCI) to dementia [1], that co-morbid depression increases the risk of dementia in type 2 diabetes [2], and that diabetes is an independent risk factor for both dementia and MCI [3]. A recent international guideline on managing diabetes in older people has been published which provides a series of recommendations on the management in patients with dementia [4].

In this chapter we try to address the significance of observations known in this area and provide a rational basis for more attention to the detection and management of changes in memory and mental performance in a setting of diabetes.

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Table 29.1 Background to the relationship between diabetes and cognitive disorders.

Professional and public concern about the impact of diabetes on cognition
Long-term influence of hyperglycemia and hypoglycemia on cerebral function unknown
Pathophysiological mechanisms involved uncertain, but may involve vascular, inflammatory, and neuronal mechanisms
No current agreement on the optimum method to detect/assess cognitive deficits in usual clinical and social care settings in individuals with diabetes
Clinical relevance of the changes observed remains uncertain

29.2 Background evidence of association between diabetes and cognitive dysfunction

The vast majority of studies in this field have been cross-sectional, often comparing a small sample of diabetes patients with diabetes-free individuals on a battery of various cognitive tests and reporting moderate differences in some – but usually not all – cognitive measures used and researchers have been aware of these limitations for some time [5]. Such studies have varied not only in the sensitivity, specificity, reliability, and validity of the tests they have employed, but also in the degree of methodological vigor they have adopted, with the tendency of studies revealing more diabetes-related cognitive deficits to have been less well-controlled [6]. Nevertheless, the overall consensus based on a review of the vast majority of such studies seems to be that:

> "… patients with type 2 diabetes have moderate impairments across all cognitive domains … a diminished ability to efficiently process unstructured information, particularly when the cognitive task at hand requires speed of response." [7]

Given the shortcoming of cross-sectional investigations, however, and the reported consensus that such studies are probably ill-equipped [7, 8] to answer the question as to whether diabetes patients are cognitively impaired, the remainder of this section relies on the findings of reviews (e.g., [9]) and systematic reviews (e.g., [10]) of longitudinal studies in demystifying the relationship between diabetes and cognition.

In one of the first prospective studies of cognitive decline in diabetes [11], the investigators examined an all-female North American sample of women as part of a wider study on osteoporotic fractures. Using a modified Mini-Mental State Examination (MMSE [12], measuring dementia), Digit Symbol Substitution (DSS [13], a measure of psychomotor speed) and Trail Making B (TMB [14], measuring sustained visual attention and mental shift), it was reported that women with diabetes were twice as likely as their diabetes-free counterparts to show major cognitive decline.

A year later, Fontbonne *et al.* [15] reported from a French sample as part of the Epidemiology of Vascular Aging Study. Having classified the study participants in terms of glycemic profile at baseline (normal fasting blood glucose, impaired (6.1–6.9 mmol/l) fasting glucose, and diabetes), they were followed up for 4 years and then assessed for a sizeable battery of cognitive tests. These tests included the TMB and DSS, as well as measures of mental flexibility and auditory attention (Paced Auditory Serial Addition Test, PASAT [16]), psychomotor speed (Finger Tapping Test [17]), verbal memory (Auditory Verbal Learning Test, AVLT [18]), visual memory (Benton Visual Retention Test, BVRT [19]), and facial recognition (Facial Recognition Test, FRT [20]). The authors reported a greater than twofold rate of cognitive impairment in people with diabetes, having controlled for confounding factors such as age, education, and gender.

In a similar set-up, Kanaya *et al.* [21] reported 4-year follow-up data from a subset of participants in the Rancho Bernardo Study, a prospective trial which had been running in California since 1972. Both men and women ($n=999$) were classified in terms of glycemic status (normal, impaired glucose tolerance, and diabetes) and assessed on three cognitive tests, namely the MMSE, TMB, and a verbal fluency test assessing semantic memory. The authors reported no age-adjusted differences in baseline cognitive function scores as a function of the glycemic group. Four years later, however, the women with diabetes had a fourfold increased risk of major cognitive decline, as evidenced in impaired verbal fluency test scores.

At about the same time, a study was conducted to assess the risk of cognitive dysfunction and development of Alzheimer's disease (AD) in a prospective study of aging and AD in 824 older (age >55 years) Catholic nuns, priests, and brothers (this was a subsample of the Religious Orders Prospective Study) [22]. The participants were followed up for approximately 5.5 years, and

had their cognitive performance assessed by a robust collection of global and specific tests. These included the MMSE, DSS, Logical Memory A (assessing ability to remember logical sequences [13]), items from the National Adult Reading Test (NART; a measure of premorbid intelligence and verbal fluency [23]), Digits Forward and Backward (assessing working memory and mental control [13]), items from the Standard Progressive Matrices (assessing visuospatial ability [24]), and many others. In appropriately adjusted analyses, the authors reported that not only did the diabetes group have lower cognitive function scores at baseline in most of the cognitive domains assessed, but that diabetes was also associated with a more rapid (by c. 44%) rate of cognitive decline in perceptual speed and a 65% increase in the risk of developing AD.

The trials reviewed above represent a small subset of several studies evaluating the link between diabetes and cognitive dysfunction, and are indicative of the overall pattern of results reported in the majority of published studies in the field. The same results have been echoed in a systematic review of prospective studies aiming to evaluate the extent to which diabetes is associated with cognitive decline and dementia [10]. This systematic review concluded that, compared to diabetes-free individuals, people with diabetes have:

- a 1.5-fold greater risk of cognitive decline
- a 1.6-fold greater risk of developing dementia
- a greater rate of decline in cognitive function.

Interestingly, the authors noted that their results had probably underestimated the deleterious effects of diabetes on cognitive function, and cited two reasons. First, the reviewed studies tended to exclude people who already had some form of cognitive impairment at baseline and therefore selectively sampled "healthier" individuals with a lower subsequent risk of cognitive decline. Second, most of the data that they reviewed failed to include information on people who died or were lost at follow-up; it is argued that success in being followed up may in itself be a result of better cognitive function and therefore discounting people who could not be followed up may have simply masked the true rate of cognitive decline in people with diabetes.

So, how might diabetes be related to cognitive decline? In type 1 diabetes, the amount and extent of exposure to hypoglycemia have been argued to be predictive of cognitive decline [25], although a meta-analysis examining the effects of type 1 diabetes on cognition failed to find evidence for this association [26].

In type 2 diabetes the picture is much more complicated; patients with the illness tend to be older and present with other co-morbidities, such as hypertension, atherosclerotic vascular disease, obesity and depression, which in themselves are independent risk factors for cognitive dysfunction. In addition, disease duration, glycemic control, socioeconomic status, age, gender, microvascular complications, insulin resistance, and the presence of ApoE $\varepsilon 4$ allele may all moderate the relationship between diabetes and cognitive dysfunction (for helpful and detailed reviews on these, the reader is referred to [7,27,28]). It is likely that the etiology is multifactorial in origin, with varying contributions from repeated hypoglycemia, long-duration hyperglycemia, amyloid deposition, insulin resistance, cerebrovascular disease, changes in the hypothalamo-pituitary axis, and inflammatory disease.

Another important factor that may exacerbate the influence of diabetes on cognitive performance is blood pressure control. Data from both the Framingham study [29] and the OCTO-Twin Study from Sweden [30] have demonstrated that, in patients with type 2 diabetes, cognitive performance is worse in the presence of hypertension or an increase in blood pressure. The Framingham cohort included patients aged 55–89 years who, over a long duration, demonstrated poorer results in logical memory scores and word fluency after an independent increase in blood pressure of 10 mmHg. In the OCTO-Twin Swedish population-based study, sequential MMSE scores over 8 years were significantly lower in the cohort of patients with both diabetes and hypertension than in the cohorts of either condition alone, or in those without either condition. This relationship between cognitive decline and the presence of either diabetes and hypertension was also observed in the Atherosclerosis Risk in Communities (ARIC) study [31] in a 6-year follow-up of almost 11,000 individuals aged 47–70 years at the initial assessment.

The fact that people with diabetes are at an increased risk of cognitive dysfunction is now accepted unequivocally. However, the precise direction of this relationship – as well as its major constituent parts – remains unexplored and hence undetermined. Is it the case that diabetes causes cognitive decline independently of the moderating factors noted above? Could cognitive decline predispose to developing diabetes? Could it be that a combination of some (or all) of the co-morbidities noted

above may cause diabetes *per se*, cognitive decline *per se*, or perhaps both? Or, finally, is the presence of other co-morbidities a moderator/mediator of a diabetes–cognitive dysfunction relationship? The jury is still out.

29.3 Background evidence of the relationship between cognitive dysfunction and glycemic control

There is evidence that impaired glucose tolerance (IGT) is associated with poorer performance in certain cognitive function scores (lower MMSE, reduced verbal fluency) and an increased risk of developing a dementing syndrome [32], although this has not been a consistent finding [33, 34]. In the Rancho Bernardo study, which included 999 Caucasian subjects aged 42–89 years with varying degrees of glucose tolerance who were followed over 4 years, a significant correlation with HbA1c level and baseline and follow-up verbal fluency scores were observed, but in women only [21].

Various studies have demonstrated a relationship between measures of glycemia and performance in cognitive assessment. The Stanford (USA) studies in patients with type 2 diabetes showed that cognitive deficits involving verbal learning and complex perceptual–motor domains were worse in those with poorer glycemic control, and that treatment with a sulfonylurea for 7 months led to significant improvements in metabolic control and tests of learning and memory [35, 36]. In another study, diabetic patients aged ≥70 years presenting to a geriatric diabetes clinic were screened for cognitive dysfunction with the MMSE and a clock-drawing test (CDT) [37]. The CDT scores were inversely correlated with HbA1c levels, which suggested that cognitive dysfunction was associated with poor glycemic control ($r=-0.38$, $p<0.004$).

The relationship between postprandial hyperglycemia (PPG) and cognitive performance was recently studied in two groups of older patients with diabetes who were treated with either rapaglinide or glibenclamide [38]. The coefficient of variation of PPG was found to be associated with MMSE scores ($r=-0.3410$, $p<0.001$) and a composite score of executive and attention functioning ($r=-0.3744$, $p<0.001$) after adjusting for multiple confounders. The results suggested that tighter control of PPG might influence the degree of cognitive decline in older patients with diabetes.

In a study of 1983 postmenopausal women (mean age 67 years) the association between HbA1c level and risk of developing cognitive impairment was determined [39]. MCI or dementia was seen subsequently to develop over a 4-year period. For each 1% increase in HbA1c level the women showed a greater age-adjusted likelihood of developing MCI (OR 1.50; 95% CI 1.14–1.97) and of developing dementia (OR 1.40; 95% CI 1.08–1.83). For those in whom the HbA1c level was ≥7%, the age-adjusted risk for developing MCI was increased almost four-fold (OR 3.70; 95% CI 1.51–9.09) and for developing dementia was increased almost three-fold (OR 2.86; 95% CI 1.17–6.98). These results clearly suggest that in older patients with IGT or diabetes the levels of glycemia and cognitive status are linked.

29.4 The importance of detecting cognitive dysfunction

Several benefits may be acquired from the early recognition of cognitive impairment in older people with diabetes (see Table 29.2), and this places emphasis on the importance of tests of cognition as part of the functional assessment of older patients. Depending on its severity, cognitive dysfunction in older diabetic subjects may have considerable implications, including increased hospitalization, less ability for self-care, less likelihood of specialist follow-up, and an increased risk of institutionalization [40].

Impaired cognitive function may result in poorer adherence to treatment, worsen glycemic control due to erratic taking of diet and medication, and increase the

Table 29.2 Benefits of early recognition of cognitive dysfunction in diabetes.

Prompts the clinician to consider the presence of cerebrovascular disease and to review other vascular risk factors
May be an early indicator of Alzheimer's disease and provide early access to medication
Allows patients and families to benefit early with social and financial planning and access to information about support groups and counseling
Creates opportunities to consider interventions for diabetes-related cognitive impairment: optimizing glucose control, controlling blood pressure and lipids

risk of hypoglycemia if the patient forgets that he or she has taken the hypoglycemic medication and repeats the dose.

29.5 Methods of detection

Cognitive dysfunction has traditionally been assessed through cognitive tests, using many different procedures ranging from single global estimates of cognitive functioning (e.g., the MMSE) to substantial batteries of neuropsychological assessments spanning the major cognitive domains of language, perception, attention, memory, visuoconstruction ability, speed of information processing, and executive (complex) functioning [20]. Some of these domains have been less well examined than others, and some tests – such as the MMSE and DSS – appear to have been used extensively when comparing people with diabetes with healthy controls. Whilst it is beyond the purpose of this chapter to describe the myriad of tests currently available to assess cognitive performance in older adults, the reader is referred to Lezak's [20] *Neuropsychological Assessment* for a compendium of hundreds of such tests.

What is of interest here is a distinction that needs to be drawn in terms of why healthcare professionals might wish to cognitively assess people with diabetes. Until now, only those studies which assess cognitive function by comparing the performance of people with diabetes to that of diabetes-free controls have been considered. However, by adopting a case-control method of assessment, conclusions can be drawn regarding the extent to which diabetes patients are in some way impaired in the respective test domain by comparing mean numerical scores in the diabetes sample with those in controls. In the absence of any established test norms, such a process allows the assessment of cognitive performance in order to compare functioning between a diabetes group and an appropriately matched control sample. So the answer to "why assess" here is to establish cross-group differences.

Informative though such comparisons may be, they are not particularly useful in a clinical setting, where it is impractical to obtain appropriate control groups or indeed standardized norms for batteries of cognitive tests. Here, clinicians might be assessing cognition to determine whether their patient is currently cognitively compromised but, given the test setting, will not have access to a control group. In such cases, the "why" behind the cognitive assessment is to establish whether further testing, referral or increased future cognitive monitoring might be necessary. In these cases, it can be argued that a significant proportion of cognitive tests which discuss the literature on diabetes and cognitive functioning renders itself beyond use, as such tests rely on comparing the patient's performance with that of others.

There are two notable exceptions to this general observation: the MMSE and the CDT. The MMSE, as the most widely used dementia screening, takes only 5–10 min to administer, and consists of questions relating to attention, orientation, memory, calculation, and language. It has been criticized as being heavily reliant on language (and as such may not be suitable for non-English speakers), but it is available in different languages. Typical tasks on the MMSE involve patients being asked to recall the year, month, date, day, and time, and to spell the word "world" backwards. They are also asked to name three objects that are in the examination room and, a few minutes later, unexpectedly to recall them. Although the MMSE is a reliable indicator of moderate to severe cognitive impairment, it is not sensitive enough to detect MCI. This may not necessarily be an issue, however, as MCI is not thought to be related to diabetes self-care activities in any significant way [41]. The MMSE is scored out of 30, with higher scores being indicative of better cognitive performance. Specifically, scores of 27–30 are regarded normal, whiles scores <26 indicate various degrees of cognitive impairment.

The CDT is another popular measure that is quick and easy to administer. Participants are given a circle (no bigger than 4–10 cm in diameter) and are told that it represents a clock face. They are then instructed to put in the numbers so that the circle now looks like a clock and, when they have done so, to set the time to 10 minutes past 11. The test assesses executive function and, in particular, the patient's ability to plan ahead, their visuospatial ability, ability to engage in abstract reasoning, and, of course, their concentration. The CDT can be scored in several ways, varying in amount of detail and precision. An extensive discussion on CDT administration and scoring is provided by Shulman *et al.* [42]. Of the several scoring methods proposed, four-point [43] or five-point [44] systems are probably the quickest and easiest. For example, when using a

five-point scoring system, the patient's drawing is assessed from being perfect (score 5) to showing inaccurate representation of 10 past 11 when the overall visuospatial organization is good (score 3), down to 0 for an inability to make any reasonable representation of a clock (for details, see [44]).

Nishiwaki *et al.* [45] have shown that, in isolation, the MMSE might not detect MCI, whilst the CDT might produce a large number of false positives. When used together, however, these tests can be reliable predictors of moderate to severe cognitive decline. Given that their administration and scoring make minimal demands in terms of time and resources, it has been argued [46] that, from a clinical point of view, they are ideal cognitive functioning screening tests for older people with diabetes. A brief mental performance test called the mini-cog has recently been piloted for use in community-dwelling older people with diabetes [47]. The mini-cog, a combination of a three-item recall and a clock drawing test (CDT), was shown to be a brief, acceptable, and practical cognitive screen for older people with diabetes when administered by a primary care nurse. It is a test that could be integrated easily into the annual diabetes review and help to identify those who may benefit from extra help with their management. More recently, a self-administered cognitive impairment test has shown some value in terms of diagnostic accuracy in a group of type 2 diabetes patients aged 70 years and over when compared with the MMSE [48].

29.6 Influence on diabetes self-care

Although many investigations have been conducted on ways to improve the patient's diabetes self-care and on their cognitive function, the relationship between the two states remains under-researched. The question here is whether cognitive functioning in diabetes patients predicts their efforts to self-manage the illness, with the implication that perhaps a poorer cognitive performance may be related to poorer self-management skills.

In one of the few studies in this area [40], an investigation was conducted as to whether cognitive impairment was associated with changes in self-care behavior and the use of health and social services in a community-based case control study of older patients with diabetes. Cognitive function was assessed using the MMSE and CDT, while self-care was assessed in two ways: (i) by counting the number of patients that were solely responsible for self-medication and blood glucose monitoring and (ii) by monitoring their attendance at a specialist diabetes clinic. Performance on the CDT showed that 65% and 72%, respectively, of diabetes patients placed the numbers and hands correctly, compared to 76% and 84% of controls. Age was found to interact with cognitive dysfunction and self-management, in that older diabetes patients were found to have worse cognitive test performance, a higher dependency, and poorer diabetes self-management.

In another study [41], 51 people with type 2 diabetes completed a battery of cognitive tests and the Summary of Diabetes Self-Care Activities questionnaire [49], but only a few associations between cognitive functioning and self-management were observed. This lack of association might have been due to the limited statistical power of the study for detecting relationships, or to the absence of any significant practical association between self-reported self-care and specific cognitive skills. One of the few significant associations that were found was the inverse relationship between self-reported memory problems (as assessed by the Subjective Memory Questionnaire [50]) and the number of diabetes problem-solving strategies (as assessed by Toobert and Glasgow's Diabetes Problem-Solving Interview), although self-reported memory complaints were not a reliable indicator of objective cognitive function. A better dietary self-management was predicted by better general (Modified Wisconsin Card Sorting Test [51]) and diabetes-specific abstract reasoning. Better exercise self-management was predicted by better scores on a test of mental flexibility, the Serial Subtractions of 7s [20], and generating more diabetes-specific problem-solving strategies was predicted by fewer subjective memory problems. The researchers assessed self-reported self-care through the Summary of Diabetes Self Care Activities (SDSCA 497]). In a later study, however, Asimakopoulou and Hampson [52] showed that the SDSCA may be prone to recall biases in people with diabetes and therefore it is suggested that self-reported self-care as assessed by instruments such as the SDSCA should be confirmed by clinical interview and opinion.

Other groups have examined self-care on the basis of medication adherence and glycemic control. For example, Rosen *et al.* [53] assessed the association between cognitive performance and adherence to oral

hypoglycemic medication, HbA1c level, and missed appointments. Cognitive function was assessed among other measures with the MMSE, TMB, and the Stroop test (this provides a measure of attention and mental flexibility, with patients being asked to read out the ink color of words spelling out incongruent color words [20]). Adherence to metformin was measured using pill bottle caps which contained a microprocessor that recorded the date and times of bottle openings; the caps were placed on the patients' prescribed antihyperglycemic medication. Age was the best predictor of medication adherence, and accounted for just under 10% of the variance in this behavior. Medication adherence was also predicted by performance on the Stroop word test and with TMB completion time, where a worse cognitive performance predicted poorer medication taking, although the amount of variance explained was only small (<10%). Interestingly, neuropsychological performance was not associated with HbA1c levels, but a poor MMSE score predicted missed appointments. These results suggested that, although cognitive performance may play a role in medication taking, it fails to explain a substantial amount of patients' variability in this behavior.

More recently, Trimble *et al.* [54] assessed the ability of the CDT to predict problematic insulin administration skills in older adults with diabetes. A group of 30 patients who had not used insulin before were taught to self-administer a sham insulin injection with an insulin pen, using a standardized protocol. The injections were continued for 7 days, after which self-administration was re-tested. An abnormal CDT was significantly associated with more problems in learning to perform the sham injections (measured as those who were unable to correctly complete all steps of the protocol or those who omitted all or part of a step), although a small number of patients with a normal CDT also demonstrated major problems. The results were in line with those of other studies, which noted the frequency of abnormal CDTs in older patients [40], and the frequency of errors in older people self-administering insulin [55]; the suggested was made that "… the CDT is a valuable predictor of potential problems with insulin administration skills in elderly patients".

Munshi *et al.* [56] assessed the relationship between global cognitive function as measured by the MMSE, CDT, and Clock in Box (CIB [57]) tests, as well as glycemic control (measured by HbA1c) in older adults with diabetes. Some 34% of patients had low scores on the CIB, and 38% had low scores on the CDT. Both the CIB and CDT were superior at identifying patients with cognitive dysfunction, compared to the MMSE. The CIB test was more sensitive in predicting poor glycemic control than the CDT, but both clock tests were inversely correlated with HbA1c levels, which suggested that cognitive function might play a role in the control of diabetes.

A cross-sectional observational study of 1398 people with diabetes, aged 60 years or older, who responded to the 2003 Health and Retirement Study Diabetes Survey [58] found that participants with greater cognitive impairment were less likely to adhere to exercise (adjusted OR (AOR) 0.725 and 0.712 for moderate and severe cognitive impairment, both $p<0.05$) and to diet (AOR 0.906 and 0.618 for moderate and severe cognitive impairment, both $p<0.01$). Cognitive impairment was associated with worse self-care.

In a recent review it was concluded that together with other diabetes complications, cognitive deficits contribute to functional impairment, increased frequency of depression-related symptoms, greater incidence of recurrent hypoglycemia, poorer adherence to treatment, and poorer prognosis [59].

Overall, it appears that the few studies which have assessed the relationship between diabetes self-management and cognition have argued for a relationship between cognitive dysfunction and impaired self-care in patients with diabetes. The amount of variance in self-care behaviors that cognitive tests seem to predict seems rather low, however, and additional patient-centered research is required in order to elucidate the relationship between cognitive dysfunction and diabetes self-management behaviors. This is particularly true with regards to the extent to which modest differences in cognitive testing might predict practical diabetes self-care skills.

29.7 The importance of excluding depression

The presence of a depressive illness may influence the outcome of any cognitive assessment in older patients with diabetes. Cognitive performance scores are likely to be diminished and create difficulties of interpretation for the clinician. Since it can be a chronic disorder with

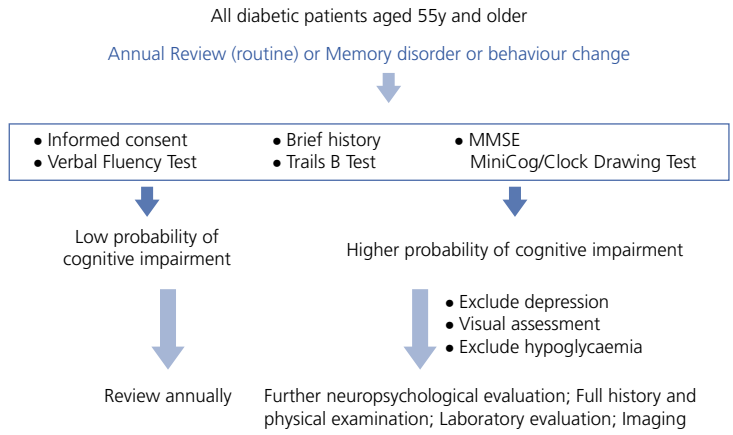

Figure 29.1 Scheme for the detection of cognitive dysfunction in type 2 diabetes mellitus.

frequent relapse, patients often have difficulty in maintaining a stable level of glycemia, and the consequent burden on caregivers can be increased substantially.

Diabetes appears to be significantly associated with depression, independent of age, gender or the presence of chronic disease [60], while the presence of diabetes appears to double the odds of developing depression [61]. In one study, the finding of depression had important implications for a group of inpatients as it was the single most important indicator of subsequent death [62]. Failure to recognize depression can be serious, since it is a long-term, life-threatening, disabling illness and can have a significant impact on the patient's quality of life [63]. Depression may be associated with worsening diabetic control and decreased treatment compliance [64].

It is important that, at the initial assessment, patients undergo a thorough history and examination and in particular are asked about any symptoms of depression. They should then undergo a mood-screening test such as the four-item Geriatric Depression Score [65] or even shorter instruments. If a significant mood disorder is detected, the opportunity presents itself to offer appropriate treatment or a referral to other specialist services.

29.8 Further investigations

The decision to investigate patients with diabetes who have observed deficits in cognition needs to be taken on the basis of history, examination, impact (if any) of deficits or behavior, personality, normal social and professional functioning, and ability for diabetes self-care management.

Whilst a full neuropsychological battery of tests will prove helpful, it is not essential in everyday clinical practice. Special techniques such as visual and somatosensory evoked potentials are too sophisticated for routine care, as is electroencephalography. Techniques such as magnetic resonance imaging (MRI), functional MRI, and single photon emission computed tomography offer exciting opportunities to equate cognitive performance with definitive evidence of structural and physiological functioning [28, 32].

A scheme for the routine screening and detection of cognitive dysfunction is shown in Figure 29.1, and this should serve as a basis for other centers to develop this approach.

29.9 Recent developments

A recent study has evaluated the relationships of long-term trajectories of glycemic control with cognitive performance in cognitively normal older people with type 2 diabetes [66]. Subjects (n =835, average age 73 years) were part of a diabetes registry where repeated HbA1c measurements were recorded over time. In this study, glycemic control trajectories predicted cognitive performance and showed that a trajectory of stable HbA1c levels over time was associated with better cognitive function.

An interesting but limited study of type 2 diabetes subjects using 72-h continuous glucose monitoring and brain imaging [67] found that higher glycemic variability was associated with lower grey matter volume. These time-scale-dependent glycemic fluctuations might be a basis for contributing to brain atrophy and cognitive outcomes within this vulnerable population.

In the Kungsholmen Project, 963 cognitively intact participants and 302 subjects with MCI and 182 with other cognitive impairment no dementia (CIND)) aged 75 years and over at baseline were followed up for 9 years to detect the incident MCI and dementia following international criteria [1]. In a Kaplan–Meier survival analysis, diabetes and pre-diabetes accelerated the progression from MCI to dementia by 3.18 years. Interestingly, the association of diabetes with the development of MCI was less evident in older people.

Based on the recognition that many deficiencies in quality care (both for dementia and diabetes) currently exist, a UK Expert Group recently published guidance on best clinical practice for managing patients with both diabetes and dementia from both a medical/diabetes perspective where patients with diabetes develop cognitive impairment and from the perspective of patients in mental health facilities developing diabetes [68].

29.10 Conclusions

In view of the high prevalence of both diabetes and dementing syndromes in aged subjects, every physician/clinician involved in providing diabetes care to this group should be familiar with this association and be skilled in the initial assessment of cognitive performance. Although the pathogenesis of cognitive dysfunction remains unclear, it can be regarded as a complication of long-duration diabetes and is likely to have an important vascular basis.

Older subjects may be particularly prone in view of other co-morbidities, which makes it essential that a cognitive assessment should form part of an initial assessment of a newly diagnosed patient with diabetes, and also part of any routine annual review.

In this respect, a familiarity with common screening methods of cognitive function would be of great help, as would an appreciation that patients with both diabetes and dementia require a different set of recommendation for guiding safe and effective diabetes [4]. This must be combined with the recognition that these individuals require greater specialist care, not less [69].

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CHAPTER 30
Mood disorders

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KEY MESSAGES

- The relationship between diabetes and depression appears to be bidirectional: diabetes and its complications lead to increased prevalence of depressive symptoms and depression leads to increased risk of diabetes.
- Diabetes and depression are interrelated: structural, functional, and neurochemical changes in the brain regions responsible for the mood may increase the risk of depression in people with diabetes.
- Screening for depression should be included in annual review assessments for older people with diabetes or earlier if self-care neglect is observed.
- Depression is treated with a combination of lifestyle modifications, pharmacotherapy, and psychotherapy in a collaborative care setting for best outcome.

30.1 Introduction

The prevalence of diabetes is increasing due to the aging of the population and increased life expectancy as a result of the decline in cardiovascular mortality [1]. The worldwide prevalence of diabetes increased with age from 12% in people aged 65–70 to 15% in those >80 years old [2] and this will double in the next 20 years [3]. In care homes, the prevalence of diabetes is even higher and affects around one-third of residents [4], therefore it appears that there is an epidemiologic shift for diabetes from being a disease of middle age to a disease of older people. Diabetes in old age is a disabling disease due to the interplay between metabolic dysfunction, vascular disease, the aging process, age-related disorders, geriatric syndromes, and frailty [5]. Diabetes in older people therefore represents a serious challenge for healthcare systems due to its chronic complications and costs. In addition to physical dysfunction, psychological complications and mood disorders such as depression, anxiety, and diabetes-related distress are common in older people with diabetes. Unlike other chronic conditions, diabetes care is dependent on patient ability to perform self-care tasks and older people with diabetes and co-morbid mood disorders are likely to be lethargic, physically inactive and less compliant with self-care responsibilities, resulting in long-term complications and increasing healthcare costs by up to 75% [6, 7]. Although mood disorders are common in older people with diabetes, they remain under-recognized and therefore untreated [8]. This chapter reviews the prevalence and management of mood disorders in older people with diabetes.

30.2 Depression

Depression is defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) as the presence of five or more of the following symptoms:

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depressed mood, reduced interest or pleasure in activities, significant weight loss or gain, decreased or increased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, reduced ability to concentrate or take decisions or recurrent thoughts of suicide nearly every day and for ≥2 weeks [9].

30.2.1 Diabetes–depression relationship

The relationship between diabetes and depression appears to be bidirectional. Diabetes and its complications lead to increased prevalence of depressive symptoms and depression leads to increased risk of diabetes. The prevalence of depression in persons with diabetes varies by the method of assessment, for example rates for depressive symptoms range from 12–27%, while rates of depressive disorders, as assessed by psychiatric interview protocols, range from 8–15% in adults with diabetes [10]. In the Health, Aging, and Body Composition Study, older people (70–79 years old) with diabetes showed increased incidence of depression compared with persons without diabetes (23.5% vs 19.0%, hazard ratio (HR) 1.31, 95% confidence interval (CI) 1.07–1.61) [11]. Diabetes is a risk factor for new-onset depression. In a meta-analysis of 16 studies to examine the risk of depression associated with diabetes, both relative risk (RR) and HR were significant at 1.27 (95% CI 1.17–1.38) and 1.23 (CI 1.08–1.40) for incident depression associated with diabetes mellitus [12]. The prevalence of depression does not appear to be uniform across people with diabetes. It has been shown that depression is common only among patients with established diabetes diagnosis rather than in those with pre-diabetes (impaired fasting glycemia or impaired glucose tolerance). Also, the prevalence is highest among those on insulin treatment or those who suffer from diabetes complications compared to those on diet or oral medications and without complications, suggesting a link between depression and advanced disease, treatment burden or poor health status [13]. Another explanation is that both diabetes complications and depression occur through a common mechanism. In a sample of 987 older people with type 2 diabetes aged ≥70 years, microvascular complications such as retinopathy and neuropathy were associated with increased depressive symptoms. These findings may have resulted from common mechanisms such as microangiopathy affecting cerebral vessels, retina and peripheral nerves or the impact of impaired visual acuity on autonomy and mood [14]. On the other hand, depression increases the risk of diabetes by 65%. In a prospective study of 4803 community adults aged ≥55 years, 379 case subjects with depression, mean (SD) age 73.6 (9.6) years, were identified. The risk of incident diabetes mellitus was higher among subjects with depression when compared with non-depressed subjects, and the association remained significant after controlling for potential confounders, including diabetes risk factors and treatment with antidepressant medications. The incidence rate was higher among depressed subjects (19.70 per 1000 person-years) relative to non-depressed subjects (12.36 per 1000 person-years). The estimated rate of diabetes mellitus attributable to depression was 6.87%. An increased risk of diabetes mellitus was also associated with depression characteristics such as non-severe depression, persistent depression, and untreated depression [15].

30.2.2 Diabetes–depression interaction

Diabetes and depression are inter-related. Structural, functional, and neurochemical changes in the brain regions responsible for mood may increase the risk of depression in people with diabetes [16]. Hyperglycemia reduces hippocampal integrity, neurogenesis, and neuroplasticity, leading to hippocampal atrophy and contributing to mood symptoms [17]. The knowledge of diabetes diagnosis, its complications, and the burden of its treatment may lead to patients feeling helpless and hopeless, which may result in depression. On the other hand, the increased rate of obesity promoting health behaviors such as physical inactivity and poor dietary habits in people with depression [18] or the increased rate of insulin resistance associated with depressive symptoms may increase the risk of incident diabetes [19]. Alternatively, diabetes and depression may share common genetic or environmental factors. Diabetes and depression may be linked through changes in biological, behavioral, neurohormonal or immuno-inflammatory pathways [20]. Low birth weight and fetal overexposure to cortisol secondary to maternal stress have been associated with hypothalamic–pituitary–adrenal (HPA) axis programming and elevated cortisol reactivity, predisposing the individual to stress and metabolic disorders [21]. Environmental factors such as poor neighborhood, increased violence, low social cohesion, poverty, poor nutrition, physical inactivity, and obesity

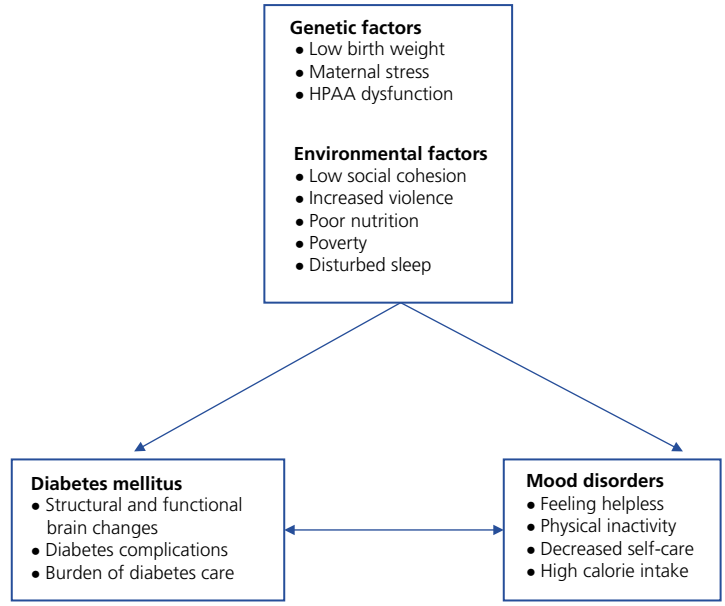

Figure 30.1 Interaction between diabetes and mood disorders: Diabetes and mood disorder share common risk factors and have a bidirectional relationship. Diabetes leads to development of mood disorders and mood disorders worsen diabetes control setting a vicious circle. HPAA, hypothalamic pituitary adrenal axis.

influence the predisposition to depression and diabetes [22]. Disturbed sleep patterns are seen in persons with depression [23] and poor sleep quality and altered circadian rhythms are associated with insulin resistance and increased risk of diabetes [24]. Although diabetes and depression are linked, no direct causal link has been identified. Depression-related biological alterations in the HPA axis, the sympathetic nervous system, and subclinical inflammation are not consistently linked with a cause and effect relationship with diabetes [25] (Figure 30.1).

30.2.3 Diagnosis

Several self-report screening tools have been developed to assist in identifying depression in older people with chronic medical conditions such as diabetes. The Patient Health Questionnaire (PHQ-9) is a brief tool that provides a two-step process to assess the presence of depressive symptoms. The first step (two questions) can be used for quick screening and it has 97% sensitivity and 67% specificity [26]. The Beck Depression Inventory-Fast Screen (BDI-FS) is a seven-item questionnaire that focuses on the affective features of depression rather than the somatic symptoms that may overlap with symptoms of diabetes [27]. The Geriatric Depression Scale-15 (GDS-15) is another tool that elicits non-somatic symptoms of depression [28]. However, depressive symptoms, such as fatigue and appetite disturbance, may be mistaken for symptoms of uncontrolled diabetes or normal aging by healthcare professionals, resulting in underdiagnosis of depression in older people with diabetes, for example only 43% of nursing home residents with a diagnosis of depression were detected by doctors [29]. Similarly, nurses were able to identify only 46% of older people with depression [30]. In primary care, doctors failed to diagnose up to 50% of older patients with depression [31]. Doctors' ability to recognize depression was significantly associated with severity of patient symptoms [32]. In a study to investigate whether diabetes nurses and endocrinologists recognized depression in 175 outpatients, mean (SD) age 56.5 (12.6) years, with diabetes the prevalence rate was 57%, but of those identified, only 43.5 were detected by staff as depressed. The only significant predictor of detection was the severity of depressive symptoms. Patient characteristics such as age or gender and illness characteristics such as duration or control of diabetes did not influence whether professionals identified depression in their patients [33]. Healthcare professionals should actively look for symptoms of depression as older people with co-morbid diabetes and depression are willing to discuss their glycemic control but are reluctant to discuss their depressive symptoms and its effects on self-care [34] (Box 30.1).

Box 30.1 Early diagnosis of mood disorders.

Screening for mood disorders should be part of the annual review and earlier if patient develops one of the following:

- non-compliance with medications
- diminished skills for performing insulin injections
- difficulties in checking own blood glucose
- reluctance to make decisions regarding adjusting insulin doses
- eating pattern becomes erratic with over- or under-eating
- significant weight gain or weight loss
- frequent or unexplained hypoglycemia
- struggling with general self-care
- non-compliance with dietary requirements
- social isolation and reluctance to seek medical care
- lack of energy and fatigue
- self-reporting symptoms of depression, for example depressed mood, insomnia or guilt
- self-reporting distress, for example frustration with diabetes care
- self-reporting anxiety, for example fear or palpitations.

30.2.4 Ethnicity

In high-income countries (HIC) depression affects around 25% of older people with diabetes [35], but in low- and middle-income countries (LMIC) the prevalence of depression appears to be higher, averaging around 35.7% [36]. Although the prevalence of diabetes is higher among ethnic minorities living in western countries, the prevalence of depression appears to be low compared with the white population. In the Diabetes and Ageing study of 115,538 older patients (aged ≥60 years, average 72 years, and 19% ≥80 years) with diabetes in the USA, the prevalence of diabetes was lowest among the white population (7%), moderate in the Chinese and Japanese (8% and 10%, respectively) populations, and highest among African Americans, Latinos, and Filipinos (14%, 14%, and 16%, respectively). The overall prevalence of depression was 17%, but Filipinos and Asians had lower rates of depression (8% and 9%, respectively) compared with African Americans (13%), Latinos (18%), and whites (20%). Asians and Filipinos tended to have the lowest prevalence of diabetes complications and geriatric conditions such as vascular complications, chronic pain, and urinary incontinence compared to the white population, which may explain the increased prevalence of depression among the whites population [37]. Another potential contributing factor to these ethnic discrepancies is the cultural differences, such as less willingness to discuss depressive symptoms among ethnic minorities [38]. In fact depression in ethnic minorities with diabetes may be under-diagnosed. In a cross-sectional study of Chinese people with diabetes living in Australia, prevalence of moderate to severe depression was found to affect 19%, but only 2% had a history of previously diagnosed depression, suggesting under-diagnosis of depression in this population. Cultural attitudes may influence the diagnosis of depression. Depression may be seen as a sign of weakness or morally unacceptable. Patients therefore may be less likely to seek help for a psychological problem or may complain of a somatic illness instead. Language barriers or social isolation may be another contributing factor to under-diagnosis of depression in ethnic minorities [39].

30.2.5 Consequences

Depression has a negative impact on patients' ability to carry out self-care responsibilities. Patients suffering from depression are likely to be physically inactive and less likely to comply with healthcare recommendations such as diet, exercise, and medications, which may lead to poor glycemic control and increased risk of diabetes complications, with reduced function and increased mortality [40].

30.2.5.1 Function

Depression tends to be associated with cognitive dysfunction, which may further compromise patients' ability to look after themselves [41]. The ACCORD-MIND study showed that depression can accelerate cognitive decline in older people with diabetes [42]. It appears that depression associated with diabetes may have a synergistic effect to increase the risk of cognitive decline based on vascular or degenerative changes. The risk of dementia increases significantly in older people with diabetes and associated depression compared to those with diabetes but without depression (HR 2.02) [43]. Similar results were found in older people with diabetes in the Mexican Health and Aging Study, with a relative risk for dementia of 2.08 and an even higher risk (2.44) in patients over the age of 80 years [44]. Physical function is also compromised by the association

of depression with diabetes. In a prospective Canadian study of 1064 older people with diabetes, mean (SD) age 59.2 (10.5) years, the risk of poor function and reduced quality of life was about three times higher (RR 2.86) for participants with four subthreshold depressive episodes compared with participants with no or minimal depression over 5-yearly follow-up assessments. The risk of poor function and reduced quality of life increased with the number of recurrent subthreshold depressive episodes even after controlling for potentially confounding variables ($p<0.001$), suggesting a dose–response relationship [45]. Depression seems to interact with function in a reciprocal way. In a prospective study of 1628 people with diabetes, mean (SD) age 60 (11) years, followed up for 3 years with annual assessments for depressive symptoms and functioning, depression and poor function were predictors of each other at the baseline, first, second, and third yearly assessment points [46].

30.2.5.2 Mortality

The combination of diabetes and depression increases the prevalence of cardiovascular risk factors such as smoking, obesity, dyslipidemia, and insulin resistance [47], therefore mortality risk increases in older people with co-morbid diabetes and depression compared to those with diabetes alone. The cardiovascular and all-cause mortality risks are 1.4 and 1.5 times, respectively, higher in patients with co-morbid diabetes and depression than in those with diabetes alone [48]. In the Nurses Health Study of 7000 women (age range 54–79), the relative risks for all-cause and cardiovascular mortality were 1.76 and 1.81, respectively, for patients with depression alone, 1.71 and 2.67 for those with diabetes alone, and 3.11 and 5.38 for co-morbid diabetes and depression [49]. The effect of depression on mortality in people with diabetes mellitus is most significant for older people. In a survival analysis to compare the strength of the association between depression and mortality between elderly and younger individuals with diabetes mellitus of 3341 persons aged ≥18 years with diabetes mellitus who participated in the Wave 2 survey of the Translating Research Into Action for Diabetes (TRIAD) study, mortality risk varied significantly with age. After controlling for the same variables, mortality risk in people ≥65 years old with depression was 78% greater than in those without. In contrast, for those <65 years old, the effect of depression on mortality was smaller and not statistically significant [50].

30.2.6 Management

Although depression is common in older people with diabetes, it remains under-recognized [8]. Depression has an adverse effect on physical and cognitive function as well as on vascular complications and mortality, therefore management of depression in older people with diabetes should be directed towards improving both psychological and physical outcomes. Improvement in psychological aspect with remission of depressive symptoms may help to improve physical functioning and medical outcomes such as glycemic control, vascular complications, and mortality. It has been shown that older people with co-morbid depression and diabetes are less likely to die within a 5-year interval if their primary care clinics are implementing depression care management programs [51]. Although the coexistence of depression with diabetes is associated with increased healthcare costs, it has been shown that systematic treatment of depression in older people with diabetes has clinical benefits without an increment in healthcare costs [52], therefore screening for depression should be included in annual review assessments for older people with diabetes or earlier if self-care neglect is observed (Boxes 30.1 and 30.2). Depression is treated with a combination of lifestyle modifications, pharmacotherapy, and psychotherapy in a collaborative care setting for best outcome (Box 30.3).

Box 30.2 Short screening tools for mood disorders.

Short screening tools can be used for rapid screening of mood disorders then detailed tests used for those who score positive.

Depression (PHQ-2) [26]

- Has patient little interest in doing things?
- Is patient feeling down, depressed or hopeless?

Anxiety (GAD-2) [81]

- Is patient feeling nervous, anxious or on edge?
- Is patient not being able to stop or control worrying?

Distress (PAID-1) [82]

- Is patient worrying about the future and the possibility of serious complications?

Box 30.3 Management of mood disorders.

Life style

- Weight loss in over-weight patients
- Exercise programs
- Tai chi mind and body exercises

Pharmacotherapy

- SSRIs are first choice
- Citalopram, sertraline, and escitalopram are well tolerated
- Treatment for at least 6 months or longer
- Long-term treatment in patients with recurrence
- Tricyclic antidepressants are associated with unfavorable side effects
- Electroconvulsive therapy is safe in severe depression

Psychotherapy

- Cognitive behavioral therapy, for example education and reducing negative attitudes
- Interpersonal psychotherapy, for example improving interpersonal relationships

Collaborative care

- Combined mood disorder and diabetes treatment through structured integrated care
- Continuous education, support, and acknowledgement of mood disorders as an integral part of diabetes care

30.2.6.1 Lifestyle

Exercise can contribute to treatment of both diabetes and depression. Intensive lifestyle intervention (ILI) designed to produce weight loss in overweight or obese patients with type 2 diabetes may reduce the risk of developing clinically significant symptoms of depression and preserve physical quality of life. In the look AHEAD (Action for Health in Diabetes) study of 5145 participants with type 2 diabetes, mean (SD) age 58.7 (6.8) years, equally randomized to ILI or usual care, ILI significantly reduced the incidence of depressive symptoms (HR 0.85, 95% CI 0.75–0.97, $P=0.02$) and preserved better function in the intervention group throughout the first 8 years ($P<0.01$) [53]. Tai chi, which involves a series of slowly performed, dance-like postures that flow into one another along with mental concentration, physical balance, muscle relaxation, and relaxed breathing, may have potential beneficial effects in improving general wellbeing and reducing depressive symptoms. It is emerging as a form of mind and body exercise that can be integrated into the prevention and rehabilitation of a number of medical and psychological conditions such as co-morbid diabetes and depression [54].

30.2.6.2 Pharmacotherapy

Selective serotonin reuptake inhibitors (SSRIs) are the preferred antidepressants in older people with co-morbid depression and diabetes due to their efficacy in ameliorating depressive symptoms without worsening glycemic control [55]. One antidepressant should normally be tried first for at least 4 weeks before switching to another SSRI or another antidepressant from a different class such as mirtazapine or venlafaxine, and treatment should be continued for at least 6 months until complete remission of depression and then stopped gradually. Long-term treatment is recommended in patients with recurrent episodes of depression to prevent relapses. No one SSRI antidepressant is more effective than another and selection should be based on patient tolerability [56]. Citalopram, sertraline, and escitalopram may be particularly well tolerated in older people due to their favorable pharmacokinetic profiles, with fewer side effects [57]. Tricyclic antidepressants (TCA) are associated with unfavorable anticholinergic side effects, confusion, hyperglycemia, orthostatic hypotension, and cardiac arrhythmias, making them a less appropriate choice for older people with depression [57]. Electroconvulsive therapy (ECT) is another safe mode of therapy in severe depression and appears to be effective and well tolerated even in frail older people [57].

30.2.6.3 Psychotherapy

There are two main forms of psychotherapy, cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT), that are effective in reducing depressive symptoms in older people with co-morbid diabetes and depression. CBT can be delivered individually by mental health providers or trained nurse case managers and mainly promotes medication adherence and self-care through education and reducing negative attitudes towards the patient's own health. IPT deals with depressive symptoms through improving interpersonal relationships. Other interventions such as increasing socialization, encouraging exercise, increasing physical function, and family support are helpful in reducing

depressive symptoms [58]. A combination of pharmacological and psychological therapy may be more effective than either alone in maintaining remission or reducing the number of recurrent episodes [59].

30.2.6.4 Collaborative care

Collaborative care where depression and diabetes treatment is combined is an important strategy. Collaborative care that incorporates brief low-intensity psychological therapy delivered in partnership with practice nurses in primary care can reduce depression and improve self-management in patients with diabetes. In a cluster randomized controlled trial of 387 patients with a record of diabetes, heart disease or both associated with depressive symptoms, mean (SD) age 58.5 (11.7), in 36 general practices in the UK, mean depressive scores were 0.23 points lower on the checklist-13 depression scale (95% CI –0.41 to –0.05) in collaborative care compared to the usual care arm after 4 months of follow-up adjusted for baseline depression score. Patients in the intervention arm also reported being better self-managers, rated their care as more patient centered, and were more satisfied with their care at follow-up [60]. In another study in four primary care networks in Canada, collaborative care, including case managers working with patients to deliver individualized care, resulted in greater 12-month improvements in PHQ-9 (7.3 (SD 5.6)) compared with control subjects (5.2 (SD 5.7), $P=0.015$). Recovery of depressive symptoms (PHQ-9 reduced by 50%) was greater among intervention patients (61% vs 44%, $P=0.03$) [61].

30.3 Anxiety

Anxiety prevalence appears to be higher in people with than those without diabetes. In a US study, the lifetime prevalence of anxiety was 19.5% in people with diabetes compared to only 10.9% in those without diabetes [62]. In a cross-sectional healthy aging in intellectual disability study among individuals ≥50 years old with intellectual disability, a significant association was found between increased anxiety symptoms and diabetes (OR 2.4, 95% CI 1.2–4.9) [63]. The relationship between diabetes and anxiety appears to be similar to that for depression, that is, bidirectional (Figure 30.1). Self-care tasks such as frequent finger pricking, blood glucose monitoring, regular medical visits, and blood sampling associated with repeated hospitalizations due to diabetes complications may be frightening and stressful for older people with diabetes, increasing the risk of anxiety. On the other hand, anxiety may cause disturbed HPAA regulation, leading to glucose intolerance, lifestyle changes, and fat accumulation, increasing the risk of diabetes [64]. A meta-analysis has demonstrated that diabetes is associated with an increased prevalence of anxiety symptoms [65], but the combination of anxiety and depressive symptoms predicted the incidence of diabetes in a large population-based study [66] and recently it has been shown that the presence of depression is important for diabetes risk to increase and the risk of diabetes caused by anxiety greatly diminishes if symptoms of depression are adjusted for in analysis [67]. A population-based cross-sectional study suggested that having both anxiety and depression was associated with the greatest risk of diabetes compared with having only one or neither condition [68]. However, anxiety and depression commonly coexist with diabetes and have a significant effect on increasing the likelihood of unhealthy lifestyle behavior, such as physical inactivity and increasing the risk of disability. In the Canadian community health survey having diabetes was associated with a greater likelihood of comorbid depression and anxiety (OR 1.99, 95% CI 1.22–3.25, $p=0.006$). For individuals with diabetes ($n=1730$), depression without anxiety (OR 2.79, 95% CI 1.39–5.62, $p=0.004$), anxiety without depression (or 3.69, 95% CI 1.34–10.11, $p=0.01$), and combined depression and anxiety (OR 4.17, 95% CI 1.66–10.51, $p=0.002$) were associated with greater disability [69]. The symptoms of anxiety may be confused with those of hypoglycemia, such as dizziness, shakiness, palpitations, and reduced coordination. Screening tools such as the Hospital Anxiety and Depression Scale [70] or the Generalized Anxiety Disorder Scale [71] can be used in addition to structured clinical interviews and patient self-reporting to make an accurate diagnosis (Boxes 30.1 and 30.2). Education programs about diabetes self-care and coping skills may help to reduce anxiety symptoms and improve diabetes control [72]. Patients with recurrent hypoglycemia are more likely to experience anxiety and panic attacks that in turn can further increase the number of episodes and may result in social isolation and negative emotional states [73]. CBT may be useful in patients on insulin therapy or those with recurrent episodes of hypoglycemia to help alleviate

feelings of worry and fear. There is evidence that collaborative care has better outcomes than usual care in alleviating anxiety symptoms [60] (Box 30.3).

30.4 Distress

Diabetes-related distress is distinctive from depression and reflects patients' worries, fears, and concerns regarding the chronic and progressive demands of diabetes, such as the burden of self-care, threats of complications, and potential loss of function [74]. Diabetes-related distress is therefore not synonymous with depression but reflects an emotional response to a demanding health-related condition. Unlike depression, which is a well-defined psychiatric condition, diabetes-related distress is linked to diabetes stressors and is viewed as part of the diabetes spectrum rather than as a separate entity indicating psychopathology [75]. Diabetes distress may include frustration with self-care and difficulties with family members or carers, leading to worsening diabetes control, which in turn leads to increasing distress, setting up a vicious circle and a bidirectional relationship between diabetes and distress (Figure 30.1). Diabetes-related distress is likely to be under-diagnosed and may be mistaken for depressive symptoms. Patients may report symptoms of depression based on their stressful experience with diabetes management and burden of self-care, leading to a high score of depressive symptoms but not high enough to reach the diagnostic threshold for depression [76]. Consequently, diabetes-related distress can be mistakenly labelled as subclinical depression or elevated depressive symptoms, therefore attention to emotional distress should be included as part of comprehensive care for older patients with diabetes, especially at critical moments which are likely to cause distress such as starting insulin therapy or the emergence of new complications [77] (Boxes 30.1 and 30.2). Distress can be measured using the Problem Areas in Diabetes (PAID) scale [78]. The PAID scale is a 20-item representative self-reported instrument for measuring diabetes-related emotional distress, and covers a range of negative emotional problems of patients with diabetes. A five-item short form of the PAID (PAID-5) was recently developed using western patients (mainly Europeans) with type 2 diabetes, with the items selected from the original pool of 20 items. The briefness of the K-PAID-5 may impose a lower burden on patients with type 2 diabetes than the full form of the instrument [79]. There is no clear evidence to suggest that interventions that target improvement of self-care management will reduce stress, suggesting that targeting distress directly is needed [80]. Continuous education, support, and acknowledgement that distress is as an integral part of diabetes care are necessary. When distress is observed, interventions specific for diabetes-related or non-diabetes-related events such as structured problem solving or family support may be helpful. It has been shown that even minimal interventions can lower levels of distress and improve disease management [81]. At higher levels of emotional distress psychotherapy may be needed (Box 30.3). Collaborative care intervention in a community study had a significantly greater reduction in diabetes-related distress than usual care ($p=0.03$) [61].

30.5 Conclusion

Mood disorders are common and seem to be under diagnosed in older people with diabetes. Mood disorders such as depression, anxiety, and diabetes-related distress tend to coexist in older people with diabetes and appear to have a bidirectional relationship, acting a risk factor and at the same time as a consequence of diabetes. To break the vicious circle of this complex bidirectional relationship between diabetes and mood disorders, early identification and treatment are important. Healthcare professionals involved in the care of older people with diabetes should therefore be aware of the associated mood disorders and the collaborative care approach that includes integrated care of both physical and mental health as appropriate.

Key points

- Diabetes prevalence is increasing in older people due to the aging of the population.
- Mood disorders such as depression, anxiety, and diabetes-related distress are common in older people with diabetes.
- The relationship between diabetes and mood disorders is bidirectional.
- A collaborative approach with integrated physical and mental health care for older people with diabetes is needed.

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CHAPTER 31
Falls and diabetes

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KEY MESSAGES

- Falls are a major health issue for older adults, especially those with type 2 diabetes.
- Diabetes is associated with an increased risk of falls, recurrent falls, and falls with serious consequences independent of traditional diabetic complications.
- Research findings support the role of diabetes as an independent risk factor for falls, and suggest specific mechanisms underlying this association.
- Although pathophysiological mechanisms are not yet fully elucidated, falls in older adults with diabetes result in poor physical, functional, economic, and quality of life outcomes.
- An assessment of the risk of falls should be incorporated into the initial evaluation of older adults with diabetes.

31.1 Introduction

"Falls" is an unusual subject to address in a diabetes textbook. Many clinical and epidemiological studies performed over recent decades have raised awareness of the role of several important conditions beyond the traditional complications of diabetes that have to be taken in account when we attend older people with diabetes. As population ages and life expectancy increases, the main focus in the care of older adults is moving from prolonging life towards increasing life expectancy free of disability, delaying the onset of dependence, and favoring the active and healthy aging. The preventive strategies to achieve this target have been centered on prevention and treatment of frailty [1–3]. Falls is one of the first clinical signs of frailty [4]. Thus, incorporating fall prevention into the care and treatment of older individuals as a gateway to frailty is critical. Currently, this concept is supported by the extensive literature demonstrating the efficacy and effectiveness of fall prevention [5, 6].

The aim of this chapter is to summarize the unique characteristics of older people with diabetes suffering from falls, reviewing why older adults with diabetes have an increased risk of falling and showing how they must be addressed in outpatient clinics.

31.2 Falls: A major public health problem

A fall is defined as an event that results in a person coming to rest inadvertently on the ground or floor or other lower level [7]. Falls are undervalued not just by the general population but also by health professionals. Nevertheless, falls are events of great clinical significance due to their high prevalence and severe consequences.

Although the incidence of falls appears to vary among countries, approximately 30–40% of people over the age of 65 years fall each year [8]. This prevalence increases to 45–50% for those over the age of 75 years.

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Among the older adults who fall, at least half of them fall more than twice yearly [8]. The most frequent consequence of falls is so-called post-fall syndrome, consisting of a "fear of falling" that may be accompanied by anxiety, restlessness, depression or confusion with physical activity [9]. Approximately 50% of the patients who fall suffer from post-fall syndrome. Although it is treatable and reversible, without any interventions it could lead to progressively avoidance of activities and reduction of physical fitness, favoring future falls, physical dysfunction, and premature nursing home admission [9]. Approximately 10% of falls result in serious injuries (fractures, head trauma or any serious soft tissue injury), 5–6% result in fractures, and 1% result in hip fractures [8]. Twelve per cent of people who fall go to the emergency department and half of them (6%) are admitted to the hospital [10]. Based on Canadian data, these admissions have a significantly longer length of stay compared to the average length of stay for other causes, indicating high-complexity admissions [10]. In addition, falls are the leading cause of accidental injury deaths in elderly people and the fifth most common cause of overall mortality [8]. Thus, the consequences of falls are devastating in terms of both health (including functionality) and economics [8–11]. The World Health Organization [12] has also recognized falls as an important public health problem, and has highlighted the need for attention towards prevention strategies. These strategies should emphasize education, training, creation of safe environments, and establishment of effective policies to reduce the risk of falls and prioritize fall-related research.

31.3 Diabetes: An independent risk factor for falls

Growing evidence suggests that diabetes mellitus may represent one of the major predictors of the risk of falling [13–15]. The Study of Osteoporotic Fractures [13], a prospective cohort study (average follow up of 7.2 years) that included 9249 women over 67 years (6.8% of them with diabetes), found that diabetes, stratified by insulin use, was associated with an increased risk of falling more than once a year (age-adjusted odds ratio (OR) 1.68, 95% CI 1.37–2.07). This risk was even higher for women treated with insulin (age-adjusted OR 2.78, 95% CI 1.82–4.24). This increased risk was due in part to a higher prevalence of previously identified risk factors for falls such as poor balance, peripheral neuropathy, arthritis, and cardiovascular disease, especially in patients with non-insulin-treated diabetes (adjusted OR 1.18, 95% CI 0.87–1.60). Another large study, the Women´s Health and Aging Study [14], showed that women with diabetes had a higher probability of any fall (after adjustments for traditional risk factors; OR 1.38, 95% CI 1.04–1.81) and multiple falls (OR 1.69, 95% CI 1.18–2.43) compared with women without diabetes. Widespread musculoskeletal pain, insulin therapy, being overweight and poor lower extremity performances were independently associated with increased likelihood of recurrent falls. In the Longitudinal Ageing Study Amsterdam [15], another population-based cohort study of 1145 (85 with diabetes) community-dwelling participants over 65 years of age were followed for a 3-year period. The results showed that the hazard ratio (HR) of recurrent falls in older people with diabetes was 1.67 (95% CI 1.11–2.51) compared to those without diabetes. After considering potential confounders (age, sex, body mass index, level of urbanization, pets in household, special adjustments at home, and alcohol and smoking status), this increased risk did not change (HR 1.63, 95% CI 1.06–2.52). Greater number of medications, musculoskeletal pain, poor self-perceived health, lower levels of physical activity and muscle strength, limitations in activities of daily living, impaired physical performance (including gait and balance), and cognitive impairment were factors that partly explained this increased risk. These findings reinforce diabetes as a risk factor for falling, providing new insights into the specific mechanisms underlying the association between diabetes and falls.

The consequences of falls are also likely to be more severe among older persons with diabetes. Falls are the most common cause of fractures [16] and there is strong evidence that the risk of fracture is increased in elderly people with type 2 diabetes [17]. This suggests that people with diabetes may be more likely to sustain a serious injury after a fall. Longitudinal data from the Health, Aging and Body Composition (Health ABC) Study [18] showed that older adults with diabetes had a higher risk of fall-related injuries requiring hospitalization compared to those without diabetes (OR 1.48, 95% CI 1.12–1.95). This risk was three times higher in patients using insulin (OR 3.00, 95% CI 1.78–5.07).

It is not completely clear why insulin-treated diabetes leads to a higher risk of falls, but the high risk of hypoglycemia associated with insulin treatment is thought to be an important factor. In a retrospective observational study of patients >65 years of age [19], outpatient hypoglycemic events were independently associated with an increased risk of fall-related fractures. In this study, the patients with type 2 diabetes who had any history of hypoglycemic event had 70% higher odds of fall-related fractures compared to those who never had a hypoglycemic event (5.24% vs 2.67%). In addition, some of the risk could be attributed to longer duration of disease and a greater prevalence of diabetes complications and other co-morbidities associated with insulin use. However, in some of the studies [13, 14], the association between insulin-treated diabetes and falls remained significant even after adjustments for traditional complications [13, 14] and duration of disease [14].

31.4 Other risk factors for falls in older adults with diabetes

Increased risk for falls in patients with diabetes can be partly explained by the coexistence of traditional diabetes complications. In the Health ABC study [20], peripheral neuropathy (OR 1.50, 95% CI 1.07–2.12), poorer vision (OR 1.41, 95% CI 0.97–2.04), and reduced renal function (OR 1.38, 95% CI 1.11–1.71) were associated with higher fall risk. Reduced balance, strength, and gait are likely intermediaries in these relationships.

Amongst traditional diabetes-related complications, diabetic neuropathies are most evaluated in their association with falls. They can affect up to 50% of people with type 2 diabetes, but they are not properly diagnosed in many cases. The most common form of neuropathy is the distal, symmetric, peripheral neuropathy (DPN), which, irrespective of age, leads to physical impairments such as slower reaction times, decreased ankle strength and mobility, greater postural instability and altered walking patterns. Several studies [21, 22] have shown DPN as an independent risk factor for both falling and repetitive falling.

Orthostatic hypotension (OH) is considered a clinical manifestation of diabetic autonomic neuropathy. Many fall-prevention programs are based on the assumed association between OH and falling, although the evidence regarding this association is currently conflicting. A cross-sectional study carried out in primary care [23] showed that OH is highly prevalent in community-dwelling older patients with type 2 diabetes (28%, 95% CI 24–33) and was not related to falling. Remarkably, orthostatic complaints were associated with previous falls (OR 1.65, 95% CI 1.00–2.72) and high fall risk (OR 8.21, 95% CI 4.17–16.19) in this study. A recent meta-analysis [24] recognized that currently insufficient data are available to enable a precise assessment of the association between orthostatic hypotension and falls. Futures studies are needed to clarify this issue. Meanwhile, it is important to test for OH by not only measuring blood pressure in the sitting and standing positions but also asking about symptoms of dizziness, light-headedness or faintness during standing.

Polypharmacy, or the use of multiple medications, is a common concern in older adults with diabetes. Management of hyperglycemia, co-morbidities, and microvascular, and macrovascular complications contribute to the use of an increased number of medications in these patients. Huang *et al.* [25] evaluated the association between the number of prescriptions and incident falls in a multi-ethnic population of older people with type 2 diabetes. They found that the individuals who experienced falls were prescribed a larger number of medications than those who did not (5.16 (3.63) vs 4.12 (3.25), $p<0.01$). After adjustments, a linear increase in the risk of falls with the prescription of four or more medications was found. Previous studies [26] have found that in older patients with diabetes antiarrhythmic medications, diuretics, digoxin, benzodiazepines, antidepressants, and antiseizure drugs were more likely to contribute to fall risk. However, in this study [25] none of the individual glucose-lowering medications conferred an increased risk of falls. One of the reasons for this lack of association with glucose-lowering agents was thought to be higher mean HbA1c of 8.34% (SD 1.85) in this population. As previously mentioned, this again raises the possibility that strict metabolic control (with higher risk of hypoglycemias) could be responsible for the increased risk of falls associated with insulin in other observational studies. Supporting this idea, Schwartz *et al.* [18] found that intensive glycemic control (HbA1c<6%) achieved with insulin therapy was associated with higher risk of falls. Other studies have shown a higher risk of falls even with oral glucose-lowering agents when associated with hypoglycemia [27] (OR 1.36, 95% CI 1.13–1.65) in people with type 2 diabetes, but this risk is higher in diabetics over 65 years (OR 1.52, 95% CI 1.18–1.95). Thus, it is clear that good

Table 31.1 Risk factors for falls and possible interventions to modify them.

Type	Risk factor	Intervention	Odds ratio (95% CI)[a]
Intrinsic factors	Age		1.7 (1.1–2.5)
	History of previous falls		3.0 (1.7–7.0)
	Gait impairment[b]	Gait training	2.9 (1.3–5.6)
	Reduced balance[b]	Balance training	2.9 (1.6–5.4)
	Use of cane or other walking aid[b]	Balance exercise Training for improving gait, learning a good used of devices	2.6 (1.2–4.6)
	Weakness or decreased strength[b]	Anaerobic exercise	4.4 (1.5–10.3)
	Cognitive impairment and/or dementia		1.8 (1.0–2.3)
	Depression		2.2 (1.7–2.0)
	Drugs (especially blood pressure medications, anti-arrhythmics and psychoactive medications[b]	Withdrawal or minimization of medications, applying evidence-based medication review checklists	2.3 (1.6–3.1)
	Reduced vision[b]	Visual impairment correction Cataract surgery Monofocal lenses	2.5 (1.6–3.4)
	Osteoarthritis		2.4 (1.9–2.9)
	Limitations in activities of daily living		2.3 (1.5–3.1)
	Deficit of vitamin D[b]	Supplementation for levels over 30 ng/ml	
Extrinsic factors	Home hazards[b]	Modification of environment	
	Inadequate footwear and foot problems[b]	Management of foot problems and footwear	

[a] These data came from observational studies, apart from vitamin D data, which were extracted from intervention studies.
[b] Modifiable risk factors.

glycemia control is a fundamental objective in all diabetic patients. However, this needs to be balanced with a safe threshold to avoid hypoglycemia and falls.

31.5 Assessment of falls in outpatient diabetes clinics

There is a growing body of evidence delineating best practices for the prevention of falls and fall-related injuries among older persons [5, 6]. These practices are different according to the setting the patient is attended (community dwelling, hospital, or nursing home). In this chapter we have focused on community-dwelling older adults with a high risk of falls. Patients with a high risk of falls are defined [28] as those who fall more than twice per year, suffer at least one fall that requires medical evaluation, or have gait and balance impairment. It has long been recognized that falls generally result from multiple, often interacting, factors. The British Geriatric Society, the American Geriatrics Society [28], the Australian Commission on Safety and Quality in Health Care [29], and the National Institute for Health and Clinical Excellence [30] each have issued guidelines on the management of falls emphasizing their multifactorial etiology. Classically, these risk factors are classified as intrinsic (specific to the individual) or extrinsic (environmental) factors (Table 31.1). Intrinsic factors are those directly related to the patients and their diseases or conditions, including co-morbidities, changes associated with aging, and acute illnesses. Extrinsic factors are those associated with the patient's environment and surroundings.

Because of the complex pathway of falls, the most effective interventions in the general population at high risk are multifactorial interventions (OR 0.70, 95% CI 0.55–0.90) [5]. These include multidimensional assessment of all possible risk factors for falls (modifiable and non-modifiable), followed by individualized intervention strategies for changing possible

Figure 31.1 The greatest potentially modifiable risk factors for falling are gait impairment, reduced balance, and weakness. Gait, posture, balance, and strength must be covered in the multidimensional assessment. Currently, multiple devices are available from simple ones such a chronometer (a) or dynamometer (b); new technological devices are being developed to make these evaluations most accurate. Posturography (c) and GaitRite (d, two photos) are more sophisticated devices.

modifiable risk factors [28] (Table 31.1). This multidimensional assessment (as detailed in [28]) is a comprehensive evaluation that includes history of falls, medication list (including over-the-counter medications), co-morbidities, gait and lower extremity joint function, neurological function, muscle strength (especially of lower extremities), cardiovascular status, visual acuity, feet and footwear, functional ability, fear related to falling, and activity of daily living skills. With specific regard to these activities, several instruments have been developed, ranging from simple devices (like a chronometer) to technologically complex instruments

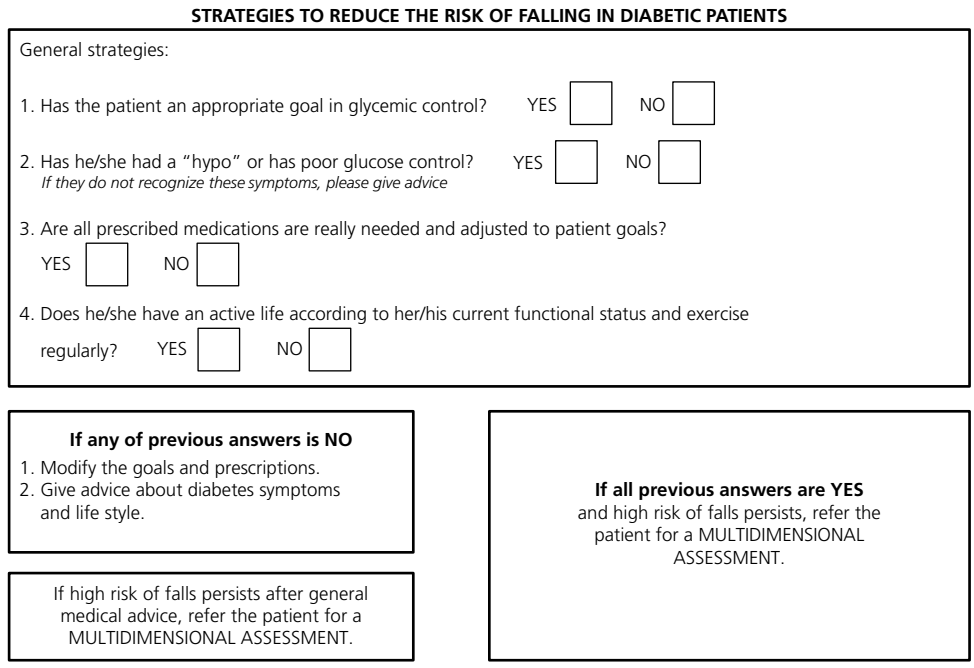

Figure 31.2 If after considering general advice the high risk of falls persists, patients must be referred to a falls and fractures clinic for a multidimensional assessment.

like the instrumented walkway (Figure 31.1). The assessment is completed by the determination of blood levels of vitamin D, parathyroid hormone, and testosterone, basic biochemistry, thyroid hormones levels, and an environmental assessment. The possible interventions include supplementation of vitamin D [31], withdrawal or minimization of psychoactive and other inappropriate medications [30], management of postural hypotension, management of foot problems and footwear, and modification of the home environment. There is also strong support for recommendations regarding exercise to improve risk of falls, in the form of resistance (strength) training and balance, gait and stretching, which are the most common modifiable factors shown in Table 31.1. Exercise should be included as part of any multifactorial intervention to prevent falls in older people.

There are very few studies evaluating specific interventions for prevention of falls in older adults with diabetes. Some studies [32, 33] have evaluated the impact of different types of exercise programs on intermediate outcomes such as leg strength, balance, walking, risk of falls, daily physical activity, etc. Extracting data from both randomized controlled trials that evaluate different interventions in general population and epidemiological studies that evaluate the association between diabetes, falls, and their risk factors, we propose a plan for diabetic elderly patients with high risk of falls.

For all older adults with diabetes, general strategies to reduce risk of falling should include the following [34] (Figure 31.2):

- Perform a detailed medication review, including all prescription as well as over-the counter medications. Try to limit the number of medications and the number of doses.
- Avoid extreme hypoglycemia and hyperglycemia.
- Establish an appropriate objective in glycemic control to minimize the risk of diabetes-related complications according to the patient's life expectancy, ensuring a safe threshold with low risk of hypoglycemia.
- Counsel patients and caregivers on the signs and symptoms of hypoglycemia and how to manage it.
- Counsel patients regarding daily physical activity based on their current functional status. In the general population without a high risk of falling, balance training exercises (such as tai chi) are a cost-effective intervention to reduce the risk of falls [6]. For patients with a high risk of falls, a multicomponent exercise program that includes resistance (strength) training,

balance and gait training, and stretching should be considered [28].

If a high risk of falls is still present after routine advice has been given, patients must be referred to a specialty clinic assessing falls and fractures to undergo a multidimensional assessment.

In summary, falls are one of the relevant consequences of diabetes in older adults. Falls risk is often neglected in the management processes (assessment, prognosis, and treatment) of these patients. This omission should be addressed, taking into account the important negative implications of falls on the quality of life of older people.

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CHAPTER 32
Managing pain

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KEY MESSAGES

- Pain is regarded as the fifth vital sign.
- Increasing age is associated with greater prevalence of pain but pain is not an inevitable part of aging.
- Many older people are reluctant to acknowledge or report pain.
- Self-report is the most reliable source of information about pain.
- Cognitive impairment is not a barrier to assessing pain; but methods other than self-report should be used.
- Pain has a significant adverse effect on physical and mental health, social relationships, self-esteem, and quality of life.
- It is important to treat the underlying cause of pain and to treat the pain itself.
- The difference between acute and chronic pain must be considered when deciding treatment.

32.1 Introduction

Historically pain was regarded as a symptom of something that needed to be treated while diagnosing the something and curing it. Understanding of pain has changed significantly over the past decade but pain remains a significant issue for many older people and their carers. Many countries have initiated national pain strategies yet pain remains under-recognized and under-treated in older people. Most pain strategies recognize the importance of screening for pain on a routine basis and using the information to trigger a formal pain assessment, management, and follow-up processes. Many older people are unable to communicate their pain or choose not to, but inability or unwillingness to communicate does not mean the person does not experience pain or require pain relief [1].

Men and women differ in the way they respond to pain and access health care. Women often report greater pain intensity, fear, and helplessness than men [2]. Likewise, cultural and pain beliefs influence the way people understand, cope with, and explain pain.

Generally, keeping the blood glucose in an acceptable, safe range for the individual is an important part of pain management in diabetes because it helps prevent unpleasant, uncomfortable symptoms associated with hypo- and hyperglycemia.

Various medical terms are used to describe pain and are shown in Table 32.1. Many common conditions that affect older people's health and cause pain, including diabetes, occur more often in older people. Many countries are becoming aware of the impact of chronic pain and the potential value of preventing pain and improving access to pain management services. In fact, chronic pain is increasingly recognized as a disease entity by relevant international organizations [3].

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Table 32.1 Pain descriptors adapted from the ISAP taxonomy [4], the American Geriatrics Society [6], the Australian Pain Society [3, 51] and the British Pain Society [5, 39].

Pain descriptor	Brief description
Allodynia	Caused by a stimulus that does not usually cause pain Involves a change in the quality of sensation
Analgesia	Absence of pain in response to a stimulus that would usually cause pain Anesthesia refers to pain in an anesthetic area/region
Causalgia	Sustained burning pain and hyperpathia after a traumatic nerve injury Vasomotor and sudomotor changes might be present and trophic changes can occur in the longer term
Dysesthesia	Abnormal unpleasant sensation
Hyperalgesia	Increased pain response to a stimulus that usually causes pain
Hyperpathia	Abnormal pain reaction to a stimulus, especially if the stimulus is repeated
Hypoalgesia	Low response to stimuli that would usually cause pain
Hypoesthesia	Reduced sensitivity to stimuli except those involving the special senses
Neuralgia	Pain along the distribution of a nerve
Neuritis	Inflammation of one or more nerves
Neuropathic	Pain due to a lesion or disease involving the somatosensory nervous system The term "neuropathic pain" is a description not a diagnosis This is a common problem in diabetes
Cancer pain	Can be caused by the cancer or by cancer treatment and may be nociceptive or neuropathic
Psychological	Psychological issues play a major role in the onset, severity, and sensation of pain but are rarely the only cause of pain Psychological factors have a significant influence on the way the individual reports pain and the impact of pain
Mixed pain	Some types of pain produce mixed sensations, e.g. headache

32.2 What is pain?

Pain is:

> "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." [4]

Importantly, pain is also defined as "what a patient says it is and where he/she says it is" [4–6]. Significantly, health professional pain taxonomy/language may not be shared or understood by older people with diabetes. Questions about pain need to be carefully worded: older people might not use the word "pain". They often use terms that refer to pain intensity and terms such as "hurt", "ache", "burning", and "sore".

Pain has also been described as the fifth vital sign [7] in an attempt to increase awareness of the importance of identifying and managing pain on the basis that vital signs are taken seriously. Since then other pain societies, health professionals, and healthcare providers have subscribed to the notion that pain is a vital sign and emphasized that it is a useful screening mechanism to identify unrelieved pain [7]. However, not all health professionals agree that pain is a vital sign. They regards signs as things that can be measured, and consider pain to be subjective and, therefore, a symptom [8].

Pain threshold refers to "the minimum intensity of a stimulus that is perceived as pain" and pain tolerance level as "the maximum intensity of pain-producing stimulus a subject is willing to accept in a given situation" [4]. Pain tolerance and thresholds differ among individuals and sometimes between episodes of pain. Pain tolerance might differ among older people and older people with diabetes. For example, research shows there is a modest increase in pain tolerance and relative absence of symptoms associated with myocardial events,

intra-abdominal infections, various types of cancer, and other acute inflammatory processes [9]. Likewise, long duration of diabetes is associated with changed sensation in peripheral and autonomic nerves. Therefore, the pain and clinical assessment and questions to the individual must be worded carefully using probing and clarifying questions.

Significantly, a higher pain threshold/tolerance does not mean the individual experiences less pain than a person with low pain threshold/tolerance. Older people often under-report their pain because they (and families and health professionals) mistakenly regard pain as a normal part of aging or because they worry their health professionals will regard them as being non-compliant [10].

32.3 Categories of pain

Generally five pain categories are described: acute, subacute, recurrent, chronic, and cancer [3, 4].

32.3.1 Acute pain

Acute pain generally arises in damaged tissue and is a normal time-limited response to trauma, accidents, or diseases and surgical procedures (procedural pain) such as debridement and/or dressing a diabetic foot wound. The American Society for Pain Management Nursing [11] expect comfort and pain and anxiety management to be considered and treated before the procedure commences on the basis that acute pain is often undertreated. Acute pain can progress to chronic pain and other adverse outcomes. Screening for pain risk, including the risk the pain could become chronic, and planning for pain relief are important prevention processes.

32.3.2 Subacute pain

Subacute pain refers to the transition process to chronic pain. The time from healing the initial injury that caused the acute pain is usually 1–2 months, to 6 months post injury.

32.3.3 Recurrent pain

Migraine is the classic recurrent pain. Recurrent pain could occur when people with diabetes and peripheral neuropathy improve their blood glucose control [12]. Pain can also occur in other joints during walking and other activates, which may lead people to restrict activities that induce pain.

32.3.4 Chronic pain

Chronic or persistent non-cancer pain refers to pain that extends beyond the normal healing time. It refers to pain that is present every in the day for more than 3 of the preceding 6 months. Chronic pain has negative effects on quality of life, work productivity, and functional status. Chronic pain is physiologically different from acute pain. It results from neuroplastic changes in the central nervous system. Nociception may have a role in some people. Chronic pain can be triggered by tissue damage in an episode of acute pain and neuroplastic changes can occur in the transition to chronic pain.

Chronic pain does not always follow an episode of acute pain and has many causes and subtypes [3, 5, 6]. Chronic pain management strategies include targeting neuroplasticity in the central nervous system. However, <10% of patients with chronic pain receive effective pain management. Pain is the worst symptom associated with chronic wounds, and pain that occurs when wound dressings are changed is worst of all [13]. There is a relationship among pain, stress, and delayed wound healing. Likewise, there is a relationship between chronic pain and social disadvantage [3].

32.3.4.1 Effects of chronic pain

The effects of chronic pain include the following:

- anatomical, functional, and chemical changes in many levels of the nervous system
- cognitive and emotional processes in the brain and spinal cord pathways that directly affect pain pathways and the individual's responses to pain (It takes longer to realign the neuroplastic changes in the brain that occur when the individual has been in pain for a long time.)
- changes in brain grey matter and cortical thickness [14]
- depression, which is also common in people with diabetes and compromises quality of life and self-care
- confusion
- sleep disturbance, for example peripheral neuropathic pain is often worse at night [12]
- increased blood pressure due to increased sympathetic pain activity and tachycardia, especially in older people with pre-existing cardiovascular disease (These factors also apply to acute pain.)
- compromised activities of daily living and diabetes self-care through fear of moving, which reduces physical activity and compromises muscle mass and

strength, postural instability, and altered gait and attention (These factors are also associated with increased falls risk [15] and mobility deficits also increase the risk of deep venous thrombosis and pressure ulcers.)
- hyperglycemia occurs through stress and anxiety associated with pain and can lead to immunosuppression and compromise wound healing, and predispose the individual to infections
- compromised food and fluid intake
- increased falls risk: falls are more common in older people in pain than those without pain [15] (People with diabetes large fiber peripheral neuropathy that leads to ataxia are 17 times more likely to fall than those without peripheral neuropathy [16]. In fact diabetes peripheral neuropathy is listed on the most commonly used falls risk assessment tools. Falls increase the risk of pain and injury-related hospital admissions and injury-related deaths [17].)
- driving risks due to mobility changes such as difficulty turning the head
- reduced quality of life (Chronic pain interferes with all aspects of an individual's life. People with chronic pain are expected to cope with the limitations imposed by the pain and the related illness/es that often lead to changes in self-concept, self-esteem, and self-identity. People may need support to find ways to cope with the pain and the changes imposed by the pain [18].)
- increased mortality [19]
- high health costs for medical care and lost productivity [3, 20].

These effects should be considered as part of the diabetes assessment for older people with diabetes. Some are partially reversible when pain is adequately managed [21].

Significantly, chronic pain is often invisible and regarded as a normal part of the disease by many older people. The invisible nature of chronic pain can result in other people questioning whether the pain actually exists, which can lead to unreported pain and fear that people will not believe they are in pain [18, 22]. These beliefs and attitudes are barriers to people reporting their pain and seeking treatment for it. They are also barriers to health professionals assessing and managing pain. Maintaining a positive identity is important to people's ability to cope with chronic pain, but is often not achieved [22]. Helping people living with chronic pain to develop and maintain a positive identity is an important aspect of pain management. It is also an important part of diabetes education empowerment strategies.

32.3.5 Cancer pain

Diabetes is associated with some forms of cancer and older people are at risk of cancer. In fact cancer is the second most common cause of death in older people and pain occurs in >70% [23, 24]. Pain is one of the most feared consequences of cancer. It can occur at any stage of the cancer journey and can be due to the effects of the cancer and/or the investigations and treatment, and is often one of many burdensome symptoms. Although the association between cancer and pain is well known, <50% of cancer patients receives effective relief [25].

It is important to realize that pain often has mixed and/or unknown causal factors and cannot be placed into neat categories.

32.4 Prevalence of pain in older people

It is difficult to determine the prevalence of pain in older people with diabetes generally, although prevalence rates for particular types of pain such as peripheral neuropathy are available. Increasing age is associated with increased prevalence of pain [3, 5, 6, 10] and many people expect to have pain as they get older, but pain is not a normal part of aging [26]. Aging is associated with an increasing number of pathologies that cause or contribute to pain as well as high rates of hospital admissions, investigations, and medical procedures, many of which are associated with acute pain. More than 20% of Australians over age 65 report having persistent pain that significantly affects their quality of life of [3]. Similar prevalence rates are reported in other countries [5, 6].

Older people generally, and those with chronic diseases and their associated complications, are known to experience pain, but pain management is ineffective in most of the world [4]. Chronic pain associated with non-malignant medical conditions is common in older adults [9]. Pain prevalence rates vary from 25% to 80% [27–29]. More than 90% of community-dwelling older people experience pain [15] and 41% report distressing, uncomfortable, "horrible", or excruciating pain [10]. Thirteen per cent of older people report strong pain and 20% state the pain interferes with their life.

Platts-Mills *et al.* [30] found that people >75 years are less likely to have their pain/pain severity documented or treated than people aged 35–45 in emergency departments (n = 88031, 7585 of whom were >75 years) even when pain management became more common over the 7-year study period (2003–2009) [30]. Older people were 19.3% less likely to receive an analgesic, 14.6% less likely to receive an opioid, and 17.5% less likely to receive NSAIDs than younger people after adjusting for pain severity, gender, and other factors. The authors suggested health professional concerns about adverse analgesic effects and a greater focus on diagnosis than pain management as some possible reasons for inadequate pain management. However, analgesia remained low, even when the person required hospital admission.

Lapane *et al.* [31] undertook a retrospective analysis of data from the database of a large for-profit nursing home chain, in which 2508 residents had pain documented on two consecutive assessments. Almost 23% had no scheduled analgesia. Older people, those with cognitive impairment, and those with Parkinson's disease were less likely to receive analgesia. Residents were more likely to receive analgesia if they reported severe pain or report pain on a daily basis. The most frequently used analgesics were opioids alone or in combination with acetaminophen. NSAIDS were prescribed for 13.8%. Changes as a result of the findings included a move towards scheduled analgesia from analgesia "as needed".

Pain is common in residents living in aged-care homes: 80% of residents in care homes have at least one pain-related condition [3, 7, 32]. Pain is a particular problem in older people with dementia and other cognitive impairments. These older people cannot advocate for their own pain relief and treatments options might be limited because of diabetes complications and co-morbidities. For example, opioids, anti-inflammatory medicines, and tricyclic antidepressant medicines are not well tolerated by older people and may be contraindicated [33].

A study of end-of-life trends between 1998 and 2010 found dying American people experienced more pain, depression, and confusion than dying people in the 1990 (interviews with 7204 proxies of people >50 years who died) [34]. Other potentially remediable symptoms included fatigue, dyspnea anorexia, and vomiting. Twenty-two per cent had cancer, 33% congestive heart failure or chronic lung disease, 16% were frail, 16% died suddenly. The prevalence of pain in the final year increased from 54.3% to 60.8%. These findings highlight the fact that persistent pain remains an issue at the end of life, which is concerning given the increasing focus on promoting comfort, relieving suffering at the end of life, and integrating palliative care into usual chronic disease care to achieve these aims.

Significantly, the prevalence of older people experiencing pain is expected to increase to one in three, 80% of whom will not have effective pain management [36]. Chronic and cancer pain are common reasons older people are unable to live independently, which further affects their quality of life, self-esteem, willingness/capacity to socialize, and mental health. Often older people are told or believe pain is part of aging; consequently many older people under-report or do not report pain, which goes unrecognized and untreated.

There is a global focus on improving pain management. The Declaration of Montreal (2010) [36] was initiated to stimulate global action to improve pain management. In the following year the General Assembly of the World Medical Association passed a resolution on the Access to Adequate Pain Management [37]. Both these documents were based on the premise that pain management is a fundamental human right and that health professionals have an ethical duty of care to undertake comprehensive clinical assessments to detect pain and to offer appropriate pain management.

32.5 Barriers to pain management

Key organizations such as the American Geriatric Society, the Australian Pain Society and the British Pain Association indicate it is essential to identify and treat pain in older people because unrelieved pain can cause despair and depression, compromise mobility, and contribute to muscle wasting, lead to social isolation, and sleep disturbances. Post-operative pain in older people is associated with confusion and delirium, fatigue, delayed healing, respiratory complications, increased length of stay in hospital, increased mortality, and costs [38]. Often medicines used to manage pain or its consequences can have adverse effects. Unrelieved pain affects the self-care capacity of people with diabetes and can contribute to hyperglycemia, which can have negative effects on pain or contribute to pain/discomfort.

However, there a number of barriers to effective pain management, including:

- ageist attitudes and not appreciating the fact that older people are not a homogenous group: they are highly individual in their life experiences, capabilities, beliefs, and expectations
- life average expectancy of people aged 85 is 6–7 years in developed countries, and older people are likely to benefit from appropriate interventions, including palliative care alone or in combination with usual care
- the general population, older people, and health professionals perpetuate myths and stereotypes about older people, pain, and old age
- health professionals and older people often have inadequate knowledge about pain, which may be a result of inadequate health professional education and education for older people with diabetes and their families about pain
- inadequate communication between health professionals and older people with diabetes who are likely to use different "pain language", and have different pain experiences, expectations and frames of reference: health professionals need to consider how their pain experiences and professional training affects the way they communicate and emphasize (or not) about pain
- difficulty accessing pain medicine or consulting with pain specialists due to mobility issues, transport problems, and when family and friends cannot advocate for older people unable to advocate for themselves, for example people with dementia
- concomitant diabetes complications and other comorbidities that affect medicine choices and/or medicine doses, including analgesics (even weak analgesics can cause side effects in older people)
- fear of causing (health professionals) or developing (older people) medicine addictions, which can lead to under-prescribing in the former and reluctance to take analgesics in the latter, and health professionals often also worry that people with addictions will "doctor shop" to obtain analgesics
- concerns about polypharmacy, medicine tolerance, and side effects
- cost of some analgesic medicines in some countries
- health-system-related barriers, including giving low priority to pain, restrictive regulation of controlled medicines, and lack of or difficulty accessing pain specialists [3, 7, 10].

These issues need to be considered when undertaking pain assessments initially and at regular intervals, and education and other strategies introduced to address them.

32.6 Common types of pain in older people

Older people with diabetes experience pain for the same reasons as older people who do not have diabetes. The most common sites where pain occurs in older people are the back, leg, knee, hip, and other joints [39]. Common types of pain include

- musculoskeletal and joint pain such as osteo- and rheumatoid arthritis
- neuropathic pain: peripheral and autonomic
- wound pain
- pruritus
- pain following amputations for foot pathology and phantom limb pain following amputations
- oral pain: gums, teeth
- gout
- cancer
- medicine-related side effects, for example muscular discomfort associated with statins
- falls and related trauma such as fractures, skin tears, and bruising
- psychological distress.

32.7 Some diabetes-specific types of pain

- Pain associated with oral cavity disease.
- Discomfort associated with hyperglycemia and hypoglycemia [40], including diabetic ketoacidosis, which is associated with abdominal pain.
- Carpel tunnel syndrome.
- Dupuytren's contracture, which occurs in 10–15% of people with diabetes and in both type 1 and type 2 diabetes, although the symptoms might be milder in people with diabetes than in the general population and occurs earlier in type 1 than in the general population [41].
- Painful peripheral neuropathy and infected foot ulcers.
- Myocardial infarction, although this may present as indigestion or be silent rather than have the classical textbooks signs of myocardial infarction [39].

32.8 Painful diabetic neuropathy

Diabetic foot disease is discussed in Chapter 10 and diabetic neuropathy and its treatment in Chapter 11. Diabetic peripheral neuropathic pain is common, affecting 16–26% of people with diabetes [42]. Polyneuropathy occurs in up to 50% of people with long duration of diabetes and is a major cause of morbidity and increased mortality [43]. However, diabetic neuropathy is often under-diagnosed and under-treated. Screening and early detection are important management strategies and can be undertaken in primary care settings and as part of the overall general and diabetes health assessment.

Screening tools include:

- Leeds Assessment of Neuropathic Symptoms and Signs
- Neuropathic Pain Symptom Inventory
- Neuropathic Pain Questionnaire
- painDETECT
- ID-pain
- Brief Pain Invetory
- NeuroQual and the Norfolk Quality of Life Scale (used to assess the effects of neuropathy on quality of life).

Neuropathic pain involves both the peripheral and central nervous systems. Diabetic neuropathy is not usually associated with muscle weakness. The pain may be transient or chronic and is typically distal, bilateral, and symmetrical, and most symptoms are felt in the feet but can extend up the leg over time [10, 42]. Symptoms include burning, shooting, stabbing and lancinating pain, paresthesia, deep aching cramp-like pain, and skin feeling hot and cold despite the temperature being normal. Hyperalgesia and allodynia are also common. The pain is often worse at night and leads to sleep disturbance and often depression. These symptoms can be present with few if any clinical signs of neuropathy. The symptoms generally resolve over 12 months but the pain should be managed. People with peripheral neuropathy are at risk of foot ulceration and regular foot assessment and foot self-care education are essential [10, 16, 42].

Improving blood glucose control might exacerbate pain initially, but is important in the longer term (Sorensen). Antiseizure medicines such gabapentin and pregabalin are often used to manage the pain but can cause drowsiness. Non-medicine options often supplement medicines, some of which should be used with caution in older people. The foot needs to be protected to prevent ulceration, pressure, heat injury, and other injuries [16].

32.9 Pressure ulcers and wound pain

Pressure ulcers are common in older people with prolonged inactivity and those living in aged-care homes where people are often frail, have nutritional deficits, and have a reduced ability to heal [44, 45]. Repositioning immobile older people can help relieve pressure but may not prevent pressure ulcers in older people with contractures and thin, frail older people and those receiving palliative care. Repositioning should not be attempted if it causes significant pain [44, 45]. The Cardiff Wound Impact Schedule can be used to determine the impact of chronic wounds and diabetic ulcers.

Several guidelines for managing pressure ulcers are available, for example those from the European Pressure Ulcer Advisory Panel, which recommend undertaking regular risk assessments. Risks include history of ulcers, advanced age, significant weight loss, eating disorders, and use of positioning devices [45]. Management includes keeping blood glucose in an acceptable target range for the individual, ensuring adequate nutrition and hydration, using nutritional supplements if indicated, and providing analgesia when needed, including before changing dressings and using non-adhesive dressings.

32.10 Managing pain

> "It is essential to assess the person with the pain rather than the pain alone." [46]

Health professionals' attitudes to pain can affect the person with diabetes. It is important that health professionals show they care and do not dismiss self-reported pain because it cannot be objectified or quantified or because the person does not use the word "pain". It is important to show empathy but to realize one person can never really know how another person's pain feels [47]. Significantly, patients are more likely to be satisfied if they feel the health professional is concerned for their welfare and is doing their best [48]. The adequacy of the education that patients receive about pain management also has a significant impact on people's satisfaction with pain treatment [49].

A number of clinical practice pain management guidelines are available to help health professionals make pain management decisions and to inform their discussions with older people with diabetes and their families about pain management. These include:

- the American Geriatrics Society guidelines [6, 57]
- the Australian National Pain Strategy [3]
- the Australian and New Zealand College of Anaesthetists (ANZCA) Guidelines for Acute Pain Management [50]
- the British Geriatric and British Pain Society UK Guideline for Managing Pain in Older People
- British Geriatrics Society guidelines for managing acute pain such as postoperative pain [39].

A key aspect of pain as the fifth vital sign strategy is increasing health professionals' attention to recognizing and adequately treating pain. The strategy encourages routine pain screening; for example asking people whether they are experiencing pain and quantifying the intensity of any pain they report using the Numeric Rating Scale. Effective pain management begins with a comprehensive history and assessment that encompasses physical, psychological, and environmental/social factors, which often overlap. It is important to treat the primary pathology, the secondary pathology, and any other contributors to pain, as well as the pain itself. Consequently a multimodal and multidisciplinary approach to pain is often needed, especially for chronic and cancer pain.

Identifying and treating pain is essential to the individual's quality of life and comfort, to reduce hospital admissions and length of stay, and prevent disability. Interestingly, health professionals vary in the way they use and interpret pain assessment scales, which can affect the pain score and treatment, particularly in hospital and aged-care homes, where several different health professionals may undertake a pain assessment on the same individual several times during the day [49]. Likewise, assessments can vary significantly between doctors and nurses caring for the same patients [48]. The impact of the differences in scoring on pain management is largely unknown.

A comprehensive pain assessment should encompass a medicine review and physical and social situations associated with the pain, effect on sleep, function, appetite, cognition, confusion, delirium, sensory loss (affects myocardial pain and peritonitis in older people as well as foot pathology) or hyperalgesia, quality of life, blood glucose pattern, and wound healing, if relevant. It is important to involve the older person, their family, and relevant health professionals in assessing the pain and deciding on care goals and a care plan [47].

Other important components of a comprehensive assessment include a clinical interview that involves asking relevant questions and using probing and clarifying questions, active listening, astute observation, and investigations if indicated. In many cases a comprehensive geriatric assessment and a medicines review are needed. As indicated, self-report should be the starting point for the pain assessment, including with older people with cognitive or communication impairments [3, 5, 6]. Some relevant questions are shown in the following list but the questions should flow from the interview rather than being a tick-box list.

Generally open questions yield more information and are more likely to reflect the older person's experiences than using closed questions that force answers. It is also important to be alert for cognitive fatigue when using pain tools and questions.

- Are you in pain now? (Bear in mind older people might not use the word "pain" and other words might be better, for example "Does it hurt anywhere?")
- Can you tell me what the pain feels like?
- Can you point to where the pain is?
- Is it there all the time? Does it go away sometimes?
- What makes the pain better?
- What makes the pain worse?
- Do you have any other symptoms besides the pain?
- Does the pain affect your sleep, usual activities, appetite, mood, visiting friends or participating in hobbies, relationships, tiredness, or quality of life? (Note: Ask about each of these issues separately.)
- Can you tell how much pain you can tolerate on a scale of 1–10?

Families can provide important information about the older person's pain, but it is important to realize the family may under- or overestimate the pain [51].

32.11 Pain tools

As indicated, self-report is the most reliable measure of pain. However, a range of tools can be used with self-report as part of a comprehensive pain assessment. Multidimensional tools can be used to assess the sensory, emotional, and physical/functional components of pain.

It is important to realize that assessing pain can be like assessing a moving target because pain can vary considerably at different times for a range of reasons [48], thus pain assessments often need to be repeated regularly. Commonly used multidimensional and unidimensional pain assessment tools are listed in the following sections.

32.11.1 Multidimensional pain-assessment tools

- McGill and Short-form McGill Questionnaires.
- Brief Pain Inventory: short and long versions are available.
- Geriatric Pain Measure.
- Pain Disability Index.
- Multidimensional Pain Inventory.

32.11.2 Unidimensional pain-assessment tools

Generally unidimensional assessment tools are used for ongoing pain assessments, including assessment of the individual's response to pain management strategies.

- Numeric Rating Scale.
- Verbal Descriptor Scale.
- Visual Analogue Scale.
- Pictorial Pain Scale/Faces Pain Scale.
- Pain Thermometer.

Numeric rating scales are poor predictors of clinically significant pain in palliative care situations [48]. Pain management based on numeric rating scales might increase patient satisfaction with treatment but it can also increase the likelihood of opioid-induced sedation and respiratory depression [48].

32.12 Observation

Some people are unable to report/communicate their pain and rely on other people, especially family and health professionals, to recognize they are in pain and to assess and treat their pain appropriately. Tools that can be used to assess pain in older people with intact motor function but who are unable to verbally report pain include the Behaviour Pain Scale and the Critical-care Pain Observation Tool (Table 32.2). They are particularly useful if they are used with tools to evaluate sedation, such as the Richmond Agitation Sedation Scale and the Sedation Agitation Scale, and tools to assess delirium, such as the Confusion Assessment Method [3].

Behavioral and other non-verbal signs might indicate pain in older people with cognitive and/or communication difficulties and might be the only indicators that the person is in pain [5]. Therefore, being familiar with the

Table 32.2 Some behavioral signs of pain that can be detected on careful observation and noting changes in the behaviors listed under relevant column subheadings in the table [51] (it is important to check assumptions that the observed behavior is a result of pain).

Facial expression	Vocal sound/ words	Body movements	Social interaction	Activities	Mental status
Frowning Frightened expression, especially when combined with vocal and body movements	Sighing Moaning Groaning Grunting Screaming	Tension Guarding	Aggressive or disruptive behavior	Change in appetite or refusing food	Cognitive changes
Grimaces, wincing, tightly closed eyes	Calling out or asking for help	Fidgeting	Inappropriate behavior	Fatigue or resting more frequently	Increased confusion
Rapid blinking	Aggression	Pacing or rocking	Reduced social interaction	Changes in sleep and rest patterns, e.g. neuropathic foot pain is often worse at night	Crying
Pulling faces, e.g. raising or lowering eyebrows, wrinkling the nose, compressed lips	Noisy breathing or panting	Restricting usual movement Changed gait	Withdrawing	Increased wandering	Irritability

older person, asking relatives/friends who know them well, and astute clinical judgement are as important as using assessment tools. It is important to consider the context in which pain might occur in these people, such as dressing a diabetic foot wound, mobilizing, or eating a meal. It is extremely important to take care interpreting behaviors as pain because they can also signify dislike of certain food types or of having a shower.

A number of observation checklists can be used to assess older people with cognitive impairment and/or communication difficulties. These include:

- the Pain Assessment Checklist for Seniors with Limited Ability to Communicate
- Pain Assessment in Advanced Dementia
- the Abbey Pain Scale
- the Non-Communicating Patient's Pain Assessment Instrument.

32.13 Pharmaceutical treatment

Treatment depends on the findings of the comprehensive assessment, and the type and cause of the pain: acute, chronic or both. Older people are more responsive to analgesic effects at equivalent blood levels and are more likely to experience side effects than younger people. Consequently, it is important to avoid analgesic medicines with long half-lives [39, 51].

Educating the older person with diabetes and/or their family carers is a key aspect of pain management. Non-medicines should be used first and/or in combination with medicines when indicated and safe. When medicines are indicated the medicine, dose, dose frequency, and dose formulation must be tailored to the older person's health status and needs, and adjusted based on regular assessments to determine the effectiveness of the pain relief and identify any side effects.

Medicines can be used prior to procedures such as wound dressings, intravenous cannulation, and rehabilitation to reduce or prevent acute pain [11, 51].

It can be challenging to achieve effective relief for chronic pain using a single medicine, thus using combinations of analgesics with different mechanisms of actions from different analgesic classes might be indicated. Combination analgesia may be more effective than NSAIDs or opioids or enable lower doses to be used, which might be important for older people with diabetes with increased risk of medicine-adverse events from these medicines [6, 39, 51].

The World Health Organization [53] devised an analgesic ladder for cancer pain that can be applied to other types of pain. The analgesic ladder consists of three steps:

1. Use non-opioids such as paracetamol or NSAIDs first.
2. If not effective add a weak opioid such as codeine for mild to moderate pain.
3. If pain persists add an opioid.

Opioids are a safer choice in frail older people because they do not have active metabolites and have a low risk of neurotoxicity [53, 54]. Opioids should not be stopped suddenly. Some older people and their families worry that opioids will cause addiction. It is important they are reassured that opioids are appropriate to treat severe pain. Fear and worry about addiction can contribute to chronic unrelieved pain.

Chronic non-malignant pain is common in older people and is best managed using regular doses of analgesics, even if the pain is not severe when the dose is due. However, NSAIDs are associated with serious life-threatening adverse events and should be used with caution and only when other therapies are ineffective, and only for short periods of time when treating non-malignant, chronic pain in older people, even when prescribed as combination analgesia [6, 55]. The American Geriatric Society recommend using acetaminophen for chronic non-malignant pain as first-line treatment in older people, even though NSAIDs are more effective for inflammatory pain.

Almost all older people are at risk of side effects from NSAIDs and opioids are often a safer choice for chronic pain relief [56, 57]. NSAIDs should only be used for 1–2 days. Optimal doses of opioids vary considerably.

32.14 Non-medicine options

Complementary and alternative therapies/medicine (CAM) may have an important role in pain management in older people with diabetes and can be used alone or with conventional analgesic medicines. Combining CAM and conventional analgesia can enable lower doses of more potent conventional analgesia to be used [58, 59]. People with diabetes are high CAM users and use often use CAM to manage diabetes complications as well as pain and to improve quality of life as well as for psychological and spiritual reasons [60].

CAM used to treat pain itself and/or to manage its consequences includes:

- mind–body therapies such as cognitive behavior and relaxation therapies, laughter
- exercise such as walking, swimming, tai chi, yoga
- massage with and without analgesic, and relaxing analgesic essential oils
- nutritional medicine
- acupuncture and acupressure
- hydrotherapy
- transcutaneous electrical nerve stimulation (TENS)
- music, including thanatology for older people who are dying
- herbal medicines such as glucosamine [51, 58, 59].

32.15 Involving the older person in pain management

It is important to encourage the older person to be actively involved in designing their pain management plan and ensuring that the pain plan is part of their overall diabetes management plan. The individual and family should have a written and/or electronic copy of the pain management plan. Older people should be encouraged to report their pain and to ask for pain relief. They should be informed that it might not be possible to totally cure/relieve their pain, but that the pain can usually be controlled.

It is important to stress the need to eat a healthy diet, remain as active as possible, continue to participate in social activities and hobbies, and to take analgesic medicines regularly to manage chronic pain, and when needed for acute pain. Patients should be encouraged to seek advice early for acute pain such as chest and abdominal pain and depression. Importantly, they should be informed that "indigestion" might be a sign of a heart attack and to seek medical attention.

It is also important to try to keep blood glucose levels within the target range to avoid the unpleasant symptoms associated with hyperglycemia and the very significant risks associated with hypoglycemia, including myocardial infarction and falls.

The diabetes sick day-care plan might need to include information about how to recognize and manage pain and/or analgesic medicines.

32.16 Communicating the pain management plan

Pain management strategies might be initiated during a hospital admission, in primary care settings or in the individual's home. Older people, their family/carers, and health professionals need clear communication about the older person's pain management plan, their diabetes care plan, and their plans for end-of-life care. The information should describe:

- pain management strategies, including medicine/s and non-medicine/s strategies
- any precautions associated with medicines or occurring as a result of limited mobility, such as driving and using motorized wheelchairs and other motorized vehicles
- possible interactions between medicines, including between conventional analgesics and CAM medicines, how to recognize them, and what action to take
- how to recognize medicine-related adverse events and what actions to take
- details about follow-up appointments and referrals
- details about any rehabilitation programs organized for the individual,
- details about whom to contact and how if pain is not controlled or other issues arise
- what to do about their pain management and medicines when older people are ill.

32.17 Pain management in aged-care homes

Many older people living in aged-care homes have pain and many also have terminal illnesses and require pain management [51, 56, 57]. Many are vulnerable for a range of reasons, including functional, sensory, and cognitive deficits including dementia, and consequently they are highly dependent on others to recognize and manage their pain. In fact, >40% of older people in aged-care homes are unable to report their pain, which often goes unrecognized and untreated, especially non-cancer pain [51]. Pain can present as agitation and/or aggression in people with dementia [61].

People with advanced dementia and those with behaviors of concern attributed to dementia are often in pain, but unable to verbally communicate their pain [62]. Dementia is a common global condition associated

with diabetes: >115 million people have dementia [63]. Pain management can help reduce agitation and possibly unnecessary prescriptions for psychotrophic medicines to manage behaviors of concern [64]. For example, 40–60% of people with dementia are treated with antipsychotics [65] despite the risk of causing stroke and death [66], and the well-documented precautions and contraindications to their use [57]. Significantly, changes in behavior should trigger a pain assessment [51].

There are many reasons for inadequate pain management in aged-care homes, including staff lack of knowledge and understanding about changed pain presentation in older people, limited knowledge about current multidisciplinary approaches to pain, limited clinical staff working in aged-care homes, and inadequate systems [51]. Pain assessments might be documented but the information might not be included in the older person's care plan.

The following principles can be applied to managing pain in aged-care homes:

- Management encourages a culture of pain awareness in staff, residents, and families.
- The aged-care facility has a systematic process for identifying and managing pain that involves:
  - educating staff, residents, and families about how to identify, report, document, and manage pain
  - using carefully worded questions to obtain self-report about pain
  - using observation to supplement self-reports, especially with people with cognitive impairment and dementia
  - using recognized validated pain assessment tools relevant to the type of pain (multidimensional/unidimensional)
  - considering pain when the individual's condition or behavior changes
  - treating pain promptly once it is identified
  - tailoring the analgesic medicine regimen to the individual's health status and needs, and using non-medicines options where possible and safe, alone or in combination with conventional analgesia
  - developing processes for collaborating with and referring to the individual's primary care doctors, pain and diabetes specialists, and other specialists as indicated
  - ensuring regular pain assessments are undertaken and documented.
- Residents are assessed for risk of pain on admission to the care home and then on a regular basis, and the findings of the assessment are used to plan an individualized pain management plan with the older person and/or their relatives if indicated.
- Analgesia is used according to relevant indications, precautions, and contraindications, is tailored to the individual's needs, and is clearly documented and monitored to determine its effectiveness, safety, and the individual's satisfaction.
- There are processes for ensuring CAM therapies are safe and provided by competent practitioners with relevant qualifications and for verifying the evidence base for any therapies used.

32.18 Summary

Pain is very common in older people generally and in those with diabetes, yet it is frequently unrecognized and untreated, which leads to significant adverse outcomes. People with cognitive impairment and who are unable to verbally communicate their pain are most at risk. Self-report is the most useful indicator pain but a range of validated pain assessment tools is available to help measure and quantify pain. It is important to ask about pain using language appropriate to the individual rather than health professional pain language and regularly reassess the pain. Non-medicine pain management strategies can be used alone or in combination with conventional approaches but must be tailored to the individual's needs, life expectancy, and risks and benefits.

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CHAPTER 33
Palliative and end-of-life care

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KEY MESSAGES

- Palliative and end-of-life care are important aspects of the diabetes disease trajectory and should be considered when undertaking annual diabetes reviews.
- The care plan, including HbA1c, blood glucose, and other targets, must be personalized according to the individual's health and functional status, medicine regimen, risk profile, and life expectancy, developed *with* the individual and sometimes with their family members, and reviewed regularly to accommodate changing health status and ensure the person's documented end-of-life care preferences are current.
- The focus of care should be on safety and promoting comfort and quality of life, and preventing avoidable harms rather than on achieving tight blood glucose control. Pharmacovigilance is essential. Preventing hypo- and hyperglycemia is important to the individual's safety, comfort, and quality of life.
- It is important to educate and support the individual and their family during the palliative/end-of-life journey and to support the family during the bereavement period after death, and respect cultural beliefs and customs and relevant regulations concerning death and dying.
- Health professionals often find it difficult to initiate discussions about palliative and end-of-life care and to decide on a management plan or to withdraw treatment in rapidly changing circumstances, especially if the person has not documented their care preferences.

"How people die remains in the memory of those who live on."

(Dame Cecily Saunders 1918–2005).

33.1 Introduction

Diabetes is an increasingly prevalent disease with a high disease burden due to complications such as cardiovascular and renal disease, and the associated effects on quality of life, pain, morbidity, and mortality [1]. Palliative care originated from the principles of autonomy and self-determination, and enables people's preferences for their life trajectory to be considered, even those people with reduced capacity to make decisions at the end of life (Box 33.1).

Epidemiological research suggests there is a strong association among obesity, diabetes, and other obesity-related diseases, including some forms of cancer [1, 2], between hyperglycemia and dementia [3], and dementia and hypoglycemia [4, 5]. Significantly, diabetes prevalence increases with increasing age and many older people have one or more complications at diagnosis.

Multimorbidity is common in diabetes: 94% of people with diabetes over age 65 have more than two co-morbidities [6]. The prevalence of co-morbidities is higher in people with psychological and social problems, which

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Box 33.1 Definition of palliative and end-of-life care.

Palliative care

Palliative care is a broad concept that encompasses end-of-life care but is not the same as end-of-life care. It is an approach that improves the quality of life of patients and families living with a life-threatening illness by relieving suffering, promoting comfort, and managing symptoms through a thorough assessment and engaging with the individual and family carers. Palliative care specialists may or may not be involved in care [8]. Palliative care can be integrated with usual care and is particularly relevant to diabetes and the associated multimorbidity [10] such as people on renal dialysis, those with heart failure, and people with non-healing foot pathology.

End-of-life care

This describes care provided to people likely to die in the following 12 months, including those for whom death is imminent, expected in a few hours or days, and those with progressive incurable disease, frailty, acute life-threatening illnesses, and existing diseases that can cause sudden death such as diabetes [21]. Three common disease trajectories have been described:

1. a relatively short period of evident decline and relatively clear difference among curative, palliative, and foreseen death trajectories, for example cancer
2. long-term limitations with intermittent exacerbations and remissions resulting in relatively sudden death, for example COPD, heart failure, and diabetes.
3. prolonged gradual deterioration towards death, for example frail older people.

The Palliative Care Outcomes Collaborative divided end-of-life care into four inter-related but non-continuous stages:

- stable
- unstable
- terminal
- Dying.

Diabetes often becomes metabolically unstable and may revert to stable or may proceed to the deteriorating stage and then stabilize again many times before the person eventually deteriorates and enters the terminal stage.

increase the mortality risk [6]. Chronic disease care is a pressing concern for most countries and proactive end-of-life planning is a key aspect of chronic disease care [7]. The Worldwide Palliative Care Alliance (WPCA), the World Health Organization (WHO) [8], and the Respecting Patient Choices Programme [9] emphasize the importance of discussing palliative and end-of-life care early in the course of chronic diseases.

Most people want to die comfortably at home, but many do not achieve their preference [10]. Their goal is more likely to be met if their end-of-life care goals and preferences are clearly documented [8]. Patient choice is an increasingly important part of current health policy. Palliative/end-of-life care aims to manage symptoms, promote comfort, enhance quality of life, provide emotional support for families, and respect the person's choices, culture, beliefs, customs, and place of dying [8, 10]. Generally the focus of care changes from curative to palliative care that aims to enhance quality of life and reduce suffering. However, the changed focus does not mean usual management is stopped.

Only one in 10 people who need or would benefit from palliative care receive such care and 25% of hospital beds are occupied by people who are dying, despite their stated preference to die at home [10]. Around 60–70% of people with chronic diseases die in hospital [11]. It is not clear what proportion of these people had diabetes because accurate data about diabetes-related deaths is difficult to obtain, possibly because diabetes is not always listed as a contributing cause of death on death certificates [12, 13]. Recording diabetes on death certificates is increasing over time [14]. Significantly, 85% of people die after a chronic, often long, illness and diabetes is the most prevalent chronic disease and is a major cause of mortality in older people [15].

An estimated 20 million people need palliative and/or end-of-life care each year. Most (69%) are over age 60, and most have chronic diseases such as diabetes and represent 90% of the burden of care, and 50% of deaths are expected because of advanced disease. In the last year of life people with long-term chronic diseases have

eight or more admissions to hospital and a 60–70% chance of dying in hospital. The average length of stay is 11.9 days: four times more than the average 3.1 days for all other admissions [10].

Diabetes-related short-term complications such as ketoacidosis (DKA) and hyperosmolar states (HHS) are associated with significant discomfort and morbidity, and can be life-threatening. Chronic hyperglycemia in the longer term increases the risk of cardiovascular disease, including heart failure, sudden death, and all-cause mortality among people with type 2 diabetes and the mortality risk may be independent of other conventional cardiovascular risk factors [16].

Palliative/end-of-life care of people with diabetes is beginning to attract the attention of clinicians and researchers but is still a neglected aspect of diabetes care [17]. Health professionals rarely discuss end-of-life care until the person has significant complications and is entering the last 6–12 months of life [17], which can deprive people of the opportunity to consider and document their preferences. Failure to discuss end-of-life care is a significant obstacle to improving the quality of dying [10].

People with diabetes require regular monitoring. Each clinical contact represents an opportunity to discuss issues important to the individual, including palliative and end-of-life care. At present most of these opportunities are missed because many diabetes and other clinicians are reluctant to discuss palliative and end-of-life care [7, 10, 18, 19], even though it is a fundamental part of caring for older people, including those with diabetes, and should be core business for healthcare services [10].

Most health professionals need education about palliative/end-of-life care and bereavement and how to conduct "difficult" conversations to increase their confidence, knowledge, and understanding of palliative and end-of-life care for older people, recognize deterioration, and facilitate their end-of-life decision-making and communication skills [10, 16]. Some experts suggest end-of-life care should be a basic health professional competency, especially in aged-care homes, to ensure people receive the care they want and need [17].

Clinicians are generally good at estimating when a person is likely to die but tend to be overly optimistic about life expectancy [20]. Importantly, not all chronic diseases have the same care trajectory or life course [10] or are as complex as diabetes. Currently, diabetes-specific indicators of poor prognosis have not been documented, although general indicators of poor prognosis and more specific indicators for cancer, renal disease, heart disease, neurological conditions, dementia, and frailty have been documented [17, 21].

The Gold Standard Framework (GSF) Prognostic Indicators [21] general indicators of poor prognosis include:

- a "Yes" response to the question "Would I be surprised if this person died in the next six to 12 months?"
- multimorbidity
- non-intentional weight loss >10% over 6 months
- general decline
- serum albumin <25 g/l
- need for assistance to perform the usual activities of daily living.

At least two of these general indicators, weight management and serum albumin, are part of usual diabetes disease monitoring. Adverse changes could indicate the need to discuss palliative/end-of-life care. Admission to an aged-care home can also be a prognostic indicator [10]: at least it should indicate the need to discuss palliative and end-of-life care.

The GSF general prognostic indicators [21] and the WPCA [8] suggest a palliative approach can be integrated with usual diabetes treatment, for example for people on renal dialysis, those with heart failure [18, 21–24], and those with non-healing chronic leg ulcers where revascularization is risky or contraindicated due to poor healing potential, compromised function, and surgical risks [23]. Despite the importance of providing diabetes-specific guidance for health professionals about end-of-life care, integrated palliative/end-of-life care is not included in most diabetes guidelines. Consequently, there is little guidance to help health professionals plan palliative/end-of-life care for/with people with diabetes and these issues may not be a significant part of specialist diabetes health professional training.

There is very little randomized control trial evidence to support diabetes palliative/end-of-life care recommendations, which could be the main reason there is limited information in most guidelines. Recently, Diabetes UK [23] and Dunning *et al.* [24] published consensus guidelines based on the best available evidence for end-of-life diabetes care, but it is not clear what impact these guidelines have had on diabetes care.

33.2 Making decisions about end-of-life care: clinical and ethical dilemmas

Some important ethical principles relevant to end-of-life care have been described [7]: clinical integrity; respect for persons, justice, and beneficence. These important principles may not be met when health professionals do not support people with diabetes to discuss palliative and end-of-life issues and to document their end-of-life care preferences (Box 33.2).

Health professionals can experience moral distress as well as personal and professional stress when people's end-of-life care needs are not clear and/or when there are different opinions about the best interests of the individual, for example there may differences in opinion among the individual, their individual and collective family members, and health professionals. Significantly, people who make end-of-life care plans have better quality of life and are more likely to have their preferred death and to die with dignity [8].

Planning for death is outside the experience of many people. Health professionals can help people with diabetes and their families think through and document their end-of-life care preferences and explain what the language used in end-of-life care documents means and what they need to do to document their care preferences [25, 26]. Such decisions are more difficult when treatment options and treatment benefit are uncertain. Helping older people document their end-of-life care preferences is consistent with modern philosophies of involving people in care decisions. When people are involved in care decisions they are more likely to adhere to treatment and self-care, outcomes improve, and health costs are reduced [25].

End-of-life care decisions are a complex mix of practical, emotional, and social interactions among people with diabetes, families, and health professionals, and may mean choosing between two equally unsatisfactory alternatives [7, 19, 27]. Many health professionals worry they will create fear, cause despair or believe that telling people the truth about their prognosis and discussing the end of life is giving bad news, and that giving bad news can cause stress and reduce wellbeing. While there is some truth in such concerns, and it is important they are acknowledged, discussing end-of-life care can enhance the person's autonomy, show respect for the individual and their choices, and acknowledge their right to accept or refuse treatment, so it is central to informed consent [7, 9, 27].

Withholding information can damage the health professional–patient relationship [28]. In contrast, providing realistic information about care options can enhance quality of life and reduce uncertainty and stress [6–10, 25, 28]. However, the approach to discussing end-of-life care must be tailored to the individual/family considering their previous experience with dying and death, and their religious and cultural beliefs and customs about death and dying.

Significantly, despite the trend toward providing more information about these issues, non-disclosure to the person about their likely health trajectory and prognosis still occurs in some countries [28]. For example, Dunning moderated a discussion about end-of-life diabetes care on the International Diabetes Federation (IDF) website in mid-2014. Most health professionals who joined the discussion were diabetes educators, endocrinologists, and psychologists, and most felt their role was to sustain hope, not to mention bad news or talk about death, regardless of the individual's health status or prognosis.

Many older people access the internet for information and join support groups as well as reading stories about other peoples' experiences with death and dying. Such personal accounts help them feel less alone and that other people understand what they are going through.

Dying has become medicalized and is often invasive even at the end of life. Most modern medical technology and medicines are used to prevent adverse events and prolong life; these aims might not be in the best interests of the individual and are not warranted for many older people at the end of life. However, there is a fine line between appropriate use of technology and aggressive unnecessary burdensome treatment [8, 10]. Many people with chronic diseases do not improve and have poor quality of life when unnecessary invasive technology and unnecessary medicines are used: a palliative approach could reduce treatment burden and improve the quality of their life and death.

Deciding on a care strategy involves health professionals:

- reflecting on the legal requirements and regulations regarding death and dying in their country and area of practice, and their own and the person with diabetes' cultural and other beliefs and experiences of death and dying

Box 33.2 Documenting end-of-life care preferences.

Regulations concerning advanced care directives/plans for end-of-life care preferences differ among countries, and in some cases within different states, territories or provinces within countries, and cultures.

Health professionals need to be familiar with or know how to access relevant information in their country. Some countries require end-of-life documentation to be signed by lawyers/notaries to reduce the risk of coercion.

Advanced care directives/preferences, sometimes called living wills, and prepaid funeral schemes encompass the individual's information about their delegated proxy decision-makers(durable power of attorney) if they do not have the capacity to decide for themselves, and their preferences for resuscitation, enteral feeding, and other management goals (blood glucose testing, stepping glucose-lowering medicines). The latter generally fall within four broad categories, which are shown in the following table.

Care goals/preferences	Management	Care relevant to the preference
No limitation of treatment	Full resuscitation, e.g. CPR, and respiratory support, e.g. intubation IV feeding through a central line	In hospital call relevant codes, MET codes (MET call)* In the community call an ambulance
Curative/restorative treatment with some limitations	**a** Not for CPR if cardiac arrest but for respiratory support, including intubation **b** Not for CPR or intubation but for active management	Codes, MET and ambulance calls No codes but MET and ambulance calls
Comfort care to manage quality of life	Not for CPR For active management that is not burdensome	Not for codes MET call to manage symptoms, e.g. IV fluids, antibiotics, pain management
Terminal care to manage comfort during the dying stage	Not for CPR, intubation, artificial feeding or admission to intensive care	Not for codes MET calls for symptom management

CPR, cardiopulmonary resuscitation; IV, intravenous; MET, medical emergency team.

* MET calls are made when specific criteria are met. The criteria generally encompass respiration, circulation, and conscious state. Some MET criteria also include signs of hypoglycemia.

Respiration

- Noisy breathing.
- Stridor.
- Change in respiratory rate <8 or >30/min.
- Acute change in pulse oximetry saturations <90% despite receiving oxygen.

Circulation

- Acute change in heart rate <40 or >130/min.
- Ischemic chest pain.
- Acute change in systolic blood pressure <90 mmHg.
- Acute change in urine output <50 ml in 4 h.

Conscious state

- Sudden change.
- Seizures.

- understanding that caring, empathy, and relieving suffering are essential elements of all care and do not mean nothing else can be done: there is always something else to do [29]
- balancing the risks and benefits of the various care options, including treatment/medicine risks and benefits, for the individual and communicating them openly to the individual
- understanding that some risk factors are not modifiable and are part of the natural history of diabetes and the related co-morbidities
- managing corticosteroid-induced hyperglycemia and the effects on bone, energy, and cognitive function
- managing nausea, vomiting, anorexia, cachexia, and weakness, which affect the counter-regulatory response to hypoglycemia and increase the falls risk
- detecting and managing hypo- and hyperglycemia, which can indicate life-threatening unstable diabetes and compromise comfort, but can often be prevented
- making appropriate medicine choices, including knowing when and how to use non-medicine options such thanatology, meditation, massage, acupuncture, and stopping unnecessary medicines
- addressing spiritual needs, which may or may not include prayer
- initiating timely discussion about end-of-life care with individuals and/or family carers before crises occur to avoid the need to make difficult decisions about terminal care when the individual's wishes are not documented
- estimating prognosis and determining whether an episode of metabolic instability can be reversed or will proceed to death
- deciding when to withdraw life-sustaining treatment, that is, when such care is no longer beneficial and becomes burdensome to the individual/family (Such decisions are more difficult if the individual/family regards treatment withdrawal as giving up on the patient and do not realize that pain and suffering can still be treated [30].)
- resolving care issues and decisions when health professionals, the individual, and family members have different opinions about the best interests of the patient, for example people with dementia and people in the terminal stage who might not be able to make decisions about their care, and those who have a documented end-of-life care plan but want to change their care preferences – if these issues are not discussed and resolved the individual's care may be suboptimal and lead to iatrogenesis and/or litigation [10, 30].

Box 33.3 Aspects of a "good" death [31].

People generally want to:
- know when death can be expected
- retain control over what happens
- die with dignity and have control over who is present at the end
- control where death occurs (people often prefer to die at home)
- know how and where to assess and understand relevant information
- have access to spiritual and emotional support when required
- be able to understand the implications and legal requirements about documenting their end-of-life preferences
- have time to say goodbye and make any provisions needed, for example for beloved pets and to ensure they have no unfinished business
- not to have life prolonged unnecessarily.

People who have an end-of-life care plan have better outcomes, families report less stress and anxiety, and there are fewer admissions to hospital and intensive care units [10]. In addition, people with dementia and those near death might not be able to make decisions about their care and the family and health professionals are unlikely to know the individual's preferences if these issues are not discussed in a timely manner. Many people with diabetes like to retain a sense of control over their care and want to participate in decisions about their care. They value being involved in care decisions and regard such involvement as a critical aspect of a "good" death [31] (Box 33.3).

33.3 Key management strategies

Like any care, palliative and end-of-life care should be personalized according to the individual's needs and desires, their end-of-life stage, the benefit and risk of any treatment options, and life expectancy. Planning care involves deciding suitable glycemic targets likely to prevent hypo- and hyperglycemia, blood pressure and lipid targets, managing medicines to achieve the targets,

and deciding when to stop medicines and withdraw other treatment [22, 24, 32]. It is important to maintain muscle strength and functional status for as long as possible, consequently nutrition and hydration are important.

Functional assessments can be a guide to increasing frailty and the need for a palliative approach and end-of-life care planning.

As indicated, diabetes can cause life-threatening emergencies during palliative care and can result in sudden death. Hypoglycemia can precipitate cardiac abnormalities, including myocardial infarction [33], as well as causing cognitive impairment that affects decision-making. The risks associated with invasive treatment might outweigh the benefits and shift the focus away from managing symptoms, promoting comfort, and maintaining quality of life [10]. It is essential to determine how the individual defines his or her quality of life and the factors that enhance their quality of life. Although valid quality of life tools are available, and have a key role in research and clinical care, they might not reflect factors that constitute quality of life for the individual, for example pets. Patient-generated quality of life tools can be developed with each individual and monitored regularly.

33.4 Pain management

Controlling symptoms and promoting comfort often involve managing pain. Managing pain is a core aspect of palliative care. Pain and discomfort can be side effects of medicines; for example constipation from opioid medications, which can be compounded by the gastrointestinal side effects of metformin and diabetes-related and other changes in the gastrointestinal tract.

Interestingly, 54% of medicines prescribed to manage severe pain in hospital in the last week of life were not administered 50% of the time [19], yet families were satisfied with the care their relatives received and indicated staff attention to comfort was "good". This finding highlights different perceptions of care and pain among health professionals, family, and the dying individual [19].

Diabetes causes or contributes to pain through organ and tissue damage, functional decline, and psychological pain and is often inadequately treated, especially in people with delirium and dementia [34]. People report bothersome pain in more than one body location that is associated with physical deficits such as reduced grip strength, unsteady gait, reduced lower limb function, muscle weakness, and fear of moving and falling [34]. In fact, pain is significantly associated with falling [34]. It is not clear whether pain is a direct cause of falls or whether falls are due to the consequences of pain, such as limited mobility.

33.5 Glycemic targets

Cardiovascular and renal diseases are leading causes of death in people with diabetes [1]. Maintaining blood glucose and blood pressure close to the normal ranges helps prevent cardiovascular disease and other diabetes complications when people have a longer life expectancy. While preventing long-term diabetes complications is not a priority of end-of-life care, managing existing complications to promote comfort and quality of life, relieve pain and other symptoms associated with complications such as foot pathology, and prevent unnecessary admissions to hospital is important, especially when the individual is metabolically stable/unstable, where recovery is likely [1, 17, 23, 24, 32].

There is little evidence for or consensus about the optimal HbA1c and blood glucose ranges or the frequency of blood glucose monitoring at the end of life. There is increasing agreement that metabolic targets must to be individualized. Recent recommended blood glucose targets are 6–11 mmol/l [23, 24], avoiding levels <6 mmol/l and >15 mmol/l [1, 23, 24, 32] and HbA1c up to 8%. These targets might not be relevant in the deteriorating and terminal stages of life. Preventing and treating the underlying causes of hyperglycemia such as infections or DKA is relevant because it causes distress and discomfort that could be alleviated [23, 24].

33.6 Monitoring blood glucose

The value of monitoring blood glucose in people with type 2 diabetes is still debated. However, blood glucose testing is important to detect hypo- and hyperglycemia. Detecting hypoglycemia can be difficult in older people, especially at the end of life, and in people with dementia because symptoms are often atypical and/or attributed to other causes and not treated [23, 24]. Some of our research that included interviews with people with

diabetes at the end of life and family members suggests many people with diabetes and their families want blood glucose monitoring to continue when they receive palliative care and at the end of life because it represents stability/familiarity in a frightening, uncertain time, and, importantly, helps them interpret symptoms [35]. Some people with diabetes and/or their families feel abandoned if blood glucose monitoring is discontinued and think staff "gave up on them".

In contrast, some health professionals believe blood glucose monitoring is painful and, unnecessary [36]. However, it is likely to be less painful than many other invasive and painful treatments used in palliative care. The frequency of blood glucose testing should be decided in consultation with the individual considering their end-of-life stage, life expectancy, medicine regimen, and whether they are prescribed diabetogenic medicines such as corticosteroids, and the individual's hypo- and hyperglycemia risk profile.

33.7 Hyperglycemia

Hyperglycemia is *not* a benign condition. It is important to manage hyperglycemia because it causes:

- distressing osmotic symptoms such as thirst, urinary frequency that leads to fluid loss and electrolyte changes, and lethargy
- calorie loss, which leads to nutritional deficits, frailty, and sarcopenia
- pain.

It also contributes to delirium and confusion, reduces mood, and adversely affects problem-solving, coping ability, and quality of life [22, 24, 32].

Significantly, hyperglycemia can be present without significant symptoms and can be missed, remain untreated and progress to DKA or HHS, which are life-threatening situations and require urgent care [37]. Dying from DKA or HHS is uncomfortable and should be prevented where possible.

People with type 1 diabetes require insulin from diagnosis. People with type 2 diabetes are often commenced on other glucose-lowering medications (GLMs) at diagnosis but many eventually require insulin due to progressive loss of β-cell function and declining insulin production: >50% people with type 2 diabetes eventually need insulin [38]. The need for insulin is usually greater in palliative/end-of-life care because diabetogenic medicines, especially corticosteroids, are frequently prescribed to manage symptoms, yet these medicines contribute to hyperglycemia.

While managing hyperglycemia to prevent long-term diabetes complications is not relevant at the end of life, it is important to enhance comfort. More frequent blood glucose testing, fluid replacement, and insulin might be indicated in unstable diabetes depending on the illness and the likely prognosis. Ketone testing should be part of the care plan for people with type 1 diabetes and very ill people with type 2 diabetes. Usual sick-day-care plans might need to be modified to suit palliative and end-of-life care situations. For example, the following could be developed:

- An optimization and maintenance plan that encompasses goals and actions, staff responsibilities, and a time scale for review.
- An escalation plan, including the signs and symptoms to observe, cues to when to investigate, and when to seek help or refer for specialist advice.
- An advanced care plan and other documents that describe care preferences and indicate when the plan should be implemented [22, 24, 32].

Families/carers may need support, frequent explanations, and education about how to recognize and manage hyperglycemia, test blood glucose and interpret the result, and how to use it to manage care, as well as the signs and symptoms that should prompt them to seek health professional advice [39].

33.8 Hypoglycemia

Hypoglycemia is a significant issue risk for many people (see Table 33.1). Hypoglycemic risk can change and needs to be assessed regularly. Hypoglycemia affects delayed and working memory in the short term, which in turn affects decision-making and problem-solving [5, 40] and can trigger myocardial infarction [33]. In the longer term it is associated with dementia [41].

As indicated, regular blood glucose monitoring is important to detect hypoglycemia, especially in people at high risk of hypoglycemia. Symptoms can differ from text book symptoms, especially in older people and those with long-standing diabetes. The changes in the counter-regulatory response such as diminished glucagon, cortisol, and growth hormone production in response to falling blood glucose levels [5, 42] means adrenergic

Table 33.1 Common hypoglycemia risk factors for older people with diabetes receiving palliative care and at the end of life: the more risk factors the person has the greater their risk of hypoglycemia.

- Prescribed GLMs, especially some sulfonylureas and insulin.
- Using medicines that interact with glucose-lowering medicines, including some herbal medicines that have hypoglycemic properties.
- Prescribed medicines that reduce appetite.
- Weight loss, malnourishment, and cachexia, which leads to reduced muscle and liver glucose stores and occurs in 40–90% of the cancer palliative care population [5]. Diminished glucose stores affect the ability to mount a counter-regulatory response, especially when counter-regulatory hormone production is also compromised.
- Swallowing difficulties and oral health problems that compromise food intake.
- Renal disease, a common complication of diabetes, affects GLM excretion. End-stage renal disease is an indicator for palliative end-of-life care.
- Macroalbuminuria.
- Liver disease, which affects GLM metabolism.
- Hypoglycemia unawareness, which is common in older people, especially those with type 1 diabetes. It may be due to autonomic neuropathy and the compromised counter-regulatory response: insufficient secretion of key counter-regulatory hormones such as glucagon [5]. Severe hypoglycemia is a significant cause of hospital admission in people >80 years with type 2 diabetes.
- Cognitive impairment and delirium, which can be a result of the aging process, chronic hypoglycemia, hyperglycemia, medicines, and dementia.
- Unmanaged pain, which affects appetite.
- Fasting for procedures or surgical interventions.
- Health professionals and family carers not recognizing hypoglycemia or mistaking hypo-/hyperglycemic coma with other causes, such as the dying process.
- Social isolation and being unable to shop for or prepare food.

symptoms might not occur and neuroglycopenic symptoms such as lethargy, confusion, and behavior changes predominate [40, 42]. It is important that health professionals learn to recognize the neuroglycopenic signs and help people with diabetes and their families learn to recognize these body cues.

Treating hypoglycemia is difficult when people have anorexia and nausea and/or vomiting because of the low glucose stores in muscle and liver, and the changed counter-regulatory response to the falling blood glucose level [40, 42]. Glucose-lowering medicines are often stopped for people who have frequent severe episodes of hypoglycemia. However, stopping glucose-lowering medicines might be inappropriate, except in the deteriorating and terminal stages, and can lead to hyperglycemia and its adverse effects, especially people with type 1 diabetes and insulin-requiring type 2 diabetes. It is also important to realize people can present in a hypoglycemic coma. Coma might not indicate impending death, but recovery is compromised if the older person is frail and/or develops hypothermia.

It is essential to undertake a comprehensive medicine review and identify and manage other hypoglycemia risk factors. Hypoglycemic risk screening can be incorporated into a comprehensive geriatric assessment (Chapter 5) but should be undertaken in all older people prescribed glucose-lowering medicines likely to cause hypoglycemia. The outcome of the risk screen can be used to plan individualized care and education. The choice of individual and combination of glucose-lowering medicines, dose, and dose frequency needs to be carefully considered to maintain blood glucose >6 mmol/l to reduce the hypoglycemia risk [22, 24, 32].

Dietetic advice can help health professionals and family/carers plan an acceptable diet and provide supplements if necessary to minimize the effects of malnutrition and minimize weight loss and its consequences, such as loss of muscle mass and strength, that predispose the individual to falls. Reversible causes of anorexia and weight loss such as dysphagia, depression, nausea, and malabsorption need to be identified and managed [43].

Complex metabolic processes that are involved in frailty, cachexia, and sarcopenia arise in palliative care situations, but vary among different disease processes and differ from cancer-related cachexia [43, 44]. Cachexia and sarcopenia are generally irreversible in advanced disease. These conditions also affect muscle glucose stores, which in turn affects the individual's capacity to mount an effective counter-regulatory response to hypoglycemia.

33.9 Medicine management

Quality use of medicines [45] is essential to achieve acceptable glycemic and other targets and minimize hypoglycemia and other medicine-related risks. Quality use of medicines involves deciding whether a medicine is needed; selecting appropriate medicine/s if a medicine is required, proactively monitoring the outcomes and stopping medicines where possible [45]. Medicine choices are influenced by their availability and cost, prognosis, health status, oral intake, medicine risk profile, co-morbidities, and whether the individual has type 1 or type 2 diabetes).

Medicines are often prescribed to treat pain and relieve suffering but the risk of medicine-related adverse events is high and can be difficult to differentiate from symptoms of terminal illness. Therefore, many medicine adverse events might not be recognized in palliative/end-of-life care [46]. In addition, people often do not volunteer symptoms or recognize the link between symptoms and medicines. Likewise, there is 10-fold difference between the number of symptoms people volunteer and symptoms identified in a comprehensive assessment [46]. The effects of aging, such as reduced thirst sensation, cognitive changes and diabetes-related changes such as neuropathy, could partly explain the difference. Some medicines that can contribute to or exacerbate symptoms are shown in Table 33.2.

The balance between medicine benefit and risk is likely to change depending on whether the individual is stable, unstable, deteriorating or terminal. Medicines may need to be stopped or the dose and dose regimen adjusted as the condition changes, sometimes frequently [46]. Key indicators that the medicine regimen should be reviewed include significant weight loss, reduced food intake, and organ failure oliguria, anuria, fever, tachycardia, and hypotension [46, 47].

33.10 Type 1 diabetes

People with type 1 diabetes do grow old. The usual insulin regimen might be appropriate in the stable phase, although the dose and dose interval might need to be adjusted if the person is not eating, loses weight, and if they have renal and liver disease to avoid hypo- and hyperglycemia. Medicines are usually ceased in the terminal stage. Most people with type 1 diabetes are prescribed basal (long/intermediate-acting)/bolus (rapid-acting) insulin regimens. Some use an insulin pump. Basal bolus regimens enable insulin doses to be adjusted to suit eating pattern (give a bolus dose when they eat) and can be particularly useful in the unstable and deteriorating stages, especially when nausea, vomiting, and anorexia are present and to prevent hyperglycemia.

Management strategies in the unstable stage depend on whether the individual is likely to return to the stable stage or deteriorate and enter the terminal stage. An intravenous insulin infusion might be indicated during acute illnesses and surgical procedures. Blood ketone tests should be performed if the blood glucose is >15 mmol/l and symptoms such as nausea, vomiting, and dehydration could indicate remediable DKA [22, 24, 32].

Insulin pumps are increasingly popular, especially among young people with type 1 diabetes. Pumps deliver a constant small basal dose of insulin and bolus doses when indicated, for example with meals, which enables flexible insulin dosing in changing situations such as palliative/end-of-life care [23]. Insulin pumps only supply low doses of rapid-acting insulin: if the pump is turned off or malfunctions, hyperglycemia can occur rapidly. Generally people who use insulin pumps are very knowledgeable about and competent to manage their pumps, but may need help during periods of instability and cognitive changes. Health professionals must have the technical expertise and competence to manage insulin pumps and seek expert advice early if they are not familiar with insulin pump therapy.

33.11 Type 2 diabetes

Like type 1 diabetes, the person's usual glucose-lowering regimen can usually be continued in the stable phase. Doses may need to be reduced or insulin commenced to reduce the medicine burden and/or reduce the risk of hypoglycemia, especially in the unstable and deteriorating end-of-life stages. Injectable medicines might be needed if the individual has difficulty swallowing oral medicines. Approximately 75% of people with diabetes have gastrointestinal problems due to malabsorption syndromes that inhibit absorption of oral medicines and gastrointestinal prokinetic medicines and reduce their effectiveness [48]. Gastrointestinal

Table 33.2 Some medicines commonly used in palliative and cancer care that can cause, exacerbate or contribute to the underlying cause of symptoms.

Medicine classes	Some common side effects/symptoms
Chemotherapy, opioids, anticonvulsants	Fatigue, which can be a symptom of hypoglycemia and hyperglycemia, nausea, vomiting, and anorexia
Corticosteroids, when withdrawing benzodiazepines, opioids and antidepressants	Anxiety Seizures Muscle cramps Insomnia
Opioids, anticholinergics, antidepressants, antipsychotics, diuretics	Dry mouth, which can be a symptom of hyperglycemia and inadequate fluid intake Constipation, delirium Urine retention/overflow (anticholinergics) Hypoglycemia with tramadol
Opioids, benzodiazepines, anticholinergics, anticonvulsants, antipsychotics, corticosteroids	Delirium Drowsiness (excluding corticosteroids), which can be a symptom of hyperglycemia
Metoclopramide, antipsychotics, opioids	Restlessness, which can be a symptom of hypoglycemia
Laxatives, cholinesterase inhibitors, antibiotics, chemotherapy	Diarrhea, which can contribute to hypoglycemia risk Muscle cramps Candida
Antidepressants, cholinesterase inhibitors, opioids, tramadol	Sweating, which can be a symptom of hypoglycemia
Opioids, anticonvulsants, antibiotics, antidepressants, antipsychotics, corticosteroids, NSAIDs, tramadol, chemotherapy	Nausea, which can be a symptom of hyperglycemia 'Bad' dreams
Opioids, chemotherapy, some anticonvulsants, antibiotics, antifungals	Vomiting, which can be a symptom of hyperglycemia or increase the risk of hypoglycemia Fluid retention Gastrointestinal bleeding
ACE, diuretics, anticholinergics, cholinergics, antipsychotics, benzodiazepines, β-agonists, alcohol, NSAIDs	Urinary incontinence, which can contribute to dehydration and hyperglycemia Alcohol can mask the symptoms of hyperglycemia
Complementary medicines	Depends on the medicine or combination of medicines and their use with conventional medicines

Medicines are essential to relieving common symptoms, but prescribing medicines to treat symptoms can lead to a prescribing cascade that increases the risk of polypharmacy, interactions, and adverse events. It can be difficult to determine which medicine/s cause the symptoms or symptom cascade because many medicines can cause the same side effects and or they can be due to non-medicine causes.

stasis can also delay glucose absorption and prolongs hypoglycemia.

The type of glucose-lowering medicine/s should suit the individual considering their renal and liver function, any medicine contraindications or precautions, their blood glucose pattern, life expectancy, self-care capacity, hypoglycemia, and their medicine-related adverse event risk profile.

Most people with diabetes are prescribed a range of other medicines such as antihypertensive and lipid-lowering medicines, and anticoagulants. The benefits and risks of continuing these medicines, doses, and dose intervals need to be reviewed to reduce the medicine burden, improve medicine safety, and reduce polypharmacy [45–47]. The unwanted gastrointestinal effects of non-steroidal anti-inflammatory medicines need to be

Table 33.3 Some issues to consider when prescribing and monitoring commonly used glucose-lowering medicines during palliative and end-of-life care.

GLM type	Some issues to consider
Metformin	Metformin is the most commonly used oral GLM, especially in overweight people Renal function needs to be monitored and metformin doses adjusted or the medicine ceased if renal function declines: creatinine > 150 mmol/l or eGFR < 30 ml/min/1.73 m^2 Metformin may be contraindicated if the person has risk factors for lactic acidosis such as respiratory disease, gastrointestinal problems, such as nausea and flatulence, and significant weight loss Metformin syrup or powder dose forms can be used when the individual has difficulty swallowing but these dose forms are expensive and have a shorter shelf life
Sulfonylureas	Sulfonylureas may be contraindicated if the person has renal and/or liver disease, which increases the risk of hypoglycemia Long-acting sulfonylureas should be avoided when the person is anorexic or has nausea, malabsorption or other hypoglycemaic risk factors
Thiazolididones	Thiazolididones are contraindicated if the person has liver and/or congestive heart failure because they cause edema, which can cause uncomfortable symptoms Pioglitazone is contraindicated in people at risk of bladder cancer and people who already have bladder cancer
Incretins	GLP-1 analogs and DPP-4 inhibitors may be appropriate for some people, but the combination of GLP-1 and sulfonylurea increases the risk of hypoglycemia GLP-1 often causes nausea and weight loss and may not be appropriate in palliative and end-of-life care Both GLP-1 and DPP-4 have been associated with pancreatitis and may not be the best choice for people with pancreatic disease They should be stopped if they cause abdominal pain
SGLT-2	There is not enough clinical experience with SGLT-2 medicines to recommend using them in palliative care situations They are associated with urinary tract and genital infections and polyuria
Insulin	The majority of people with type 2 diabetes eventually require insulin and may already be on insulin when they commence palliative care Insulin doses are easier to adjust than oral GLMs Small dose of rapid-acting insulin can be given when the individual eats and a low basal dose can control hyperglycemia due to stress and the disease process Initiating insulin can reduce the tablet burden and simplify the medicine regimen but does have a significant hypoglycemia risk

SGLT-2, sodium-glucose cotransporter-2 inhibitors.

considered when the individual is anorexic or using corticosteroids and some other medicines. Table 33.3 shows some commonly used glucose-lowering medicines and some of the issues that can be considered before prescribing these medicines.

33.12 Complementary and alternative therapies

"Complementary" means integrating complementary and alternative medicine (CAM) and "alternative" means using CAM instead of conventional treatment/medicines [49].

People with diabetes frequently use CAM [50, 51]. Likewise, people receiving palliative/end-of-life care often use CAM to relieve pain, maintain comfort and quality of life, and address their spiritual needs to achieve a "good" death [52]. Sometimes CAM is used to promote sleep and reduce restlessness, agitation, and mental stress [53, 54].

People often self-prescribe or are prescribed one or more of the following CAM [54]:

- herbal medicines
- massage, with and without essential oils
- music therapy such as thanatology
- guided imagery and meditation

- essential oils (aromatherapy), which can be administered in vaporizers, baths or massage, or in some countries they may be administered orally
- acupuncture, acupressure, and reflexology
- pet therapy and creative therapeutic writing
- art therapy.

There is continuing debate in some countries, for example Australia, about the value and safety of legalizing medical cannabis, which is legal in other countries and is used to control pain and seizures. Thus, it is important to ask about CAM use and consider the possibility of CAM–conventional medicine interactions [55] such as bleeding (St John's wort), voiding difficulty (St John's wort) and diuresis (guarana) [46].

33.13 Nutrition and hydration

People receiving palliative care often develop anorexia, cachexia sarcopenia, and dysphagia. People with diabetes are often deficient in essential nutrients and/or are anemic, especially in the presence of renal disease. Metformin inhibits absorption of vitamin B_{12}, consequently some older people may require supplementary nutrients and protein supplements [56]. Restricting carbohydrate is impractical and usually unnecessary.

When people can no longer consume enough food and fluids orally, they might require enteral feeds to sustain energy reserves and provide essential nutrition and fluids. However, the risks and benefits, including the risk of accelerating death, must be considered before commencing enteral feeds. For example, people with significant hypoglycemia risk and renal disease might benefit from extra calories to minimize the hypoglycemia risk in the stable phase. However, enteral feeding is not likely to improve nutritional or functional status, quality of life or survival in people with advanced disease. Enteral feeding-related risks include nausea, bloating, and diarrhea, which compromise comfort and quality of life [57]. People's preferences for enteral nutrition can be included in their end-of-life care plan.

People who are actively dying do not usually experience hunger, possible due to ketone production that occurs during starvation. They may experience thirst, but thirst is not quenched by artificial hydration [57]. Mouth care should be provided to alleviate dry mouth.

33.14 Diabetogenic medicines

Some medicines affect glucose homeostasis and cause/exacerbate hyperglycemia in people with diagnosed diabetes and predispose those at risk of diabetes to diabetes [58–60]. Corticosteroids are used in 30–60% of palliative care patients for a range of reasons, including management of edema in some tumors, spinal cord compression, anorexia, weight loss, fatigue, and wellbeing [61]. Hyperglycemia is proportional to the dose, dose formulation, dose regimen, and duration of treatment with corticosteroids [62]. Short courses may not cause hyperglycemia or only have a short-term effect on the blood glucose. Box 33.4 outlines some of the mechanisms that account for the diabetogenic effects of corticosteroids.

Screening people for and educating them about their risk of hypoglycemia before prescribing diabetogenic medicines such as corticosteroid, antipsychotic medicines, thiazide diuretics, and corticosteroids helps identify the likelihood the individual will develop corticosteroid-induced hyperglycemia. An appropriate blood glucose monitoring regimen will enable treatment to be initiated early to reduce the impact of hyperglycemia on comfort, cognitive function, and other symptoms.

Box 33.4 Some proposed explanations for the diabetogenic effects of corticosteroid medicines.

Corticosteroid medicines:

- enhance gluconeogenesis in the liver by up-regulating key hormones that contribute to hyperglycemia, such as glucose-6-phoshatase and phosphoenolpyruvate carboxylase
- suppress insulin release from the β-cells in the pancreas
- induce peripheral insulin resistance by inhibiting the production of glucose transporters in adipose and skeletal muscle cells: insulin resistance and impaired glucose tolerance can occur within 48 h of commencing corticosteroids
- contribute to fasting and postprandial hyperglycemia: a daily dose administered in the morning tends to cause hyperglycemia in the late afternoon or early evening.

Once these pathophysiological changes occur, recovery can take days.

Corticosteroids must not be stopped suddenly. The doses must be reduced gradually.

Corticosteroids can mask the signs and symptoms of infections and complicate symptom identification because the signs and symptoms of infections are often atypical in people with diabetes. The skin can become thin, fragile, and prone to tears, especially in older people, which can cause considerable discomfort and distress. Corticosteroids also have variable effects on bone formation and reduce calcium absorption, which increases the risk of osteoporotic fractures and pain [63]. Mental changes range from mild psychosis to significant psychiatric pathology and might be difficult to distinguish from delirium and other cognitive changes [63].

33.15 Managing corticosteroid-induced diabetes in palliative and end-of-life care

The aim of management is to balance the benefits of using corticosteroid medicines with their effects on glucose homeostasis by assessing:

- individual susceptibility to hyperglycemia and psychological effects
- the blood glucose pattern: corticosteroids often cause hyperglycemia in the afternoon
- meal times
- proposed corticosteroid type, dose, and dose schedule: intermittent or continuous
- the diabetogenic effects of individual corticosteroids: choose the least diabetogenetic medicine and use it for the shortest time to limit the effects on glucose variability, prevent DKA and HHS, and limit the care burden on the individual and their family/carer
- when to cease the corticosteroid: this usually involves slowly reducing doses and adjusting insulin and other glucose-lowering medicine doses to prevent hypoglycemia [23, 24, 59].

Management consists of monitoring blood glucose, especially in the afternoon, but more frequently if insulin is prescribed, and proactively adjusting insulin doses to reduce hyperglycemia. People managed using diet may require medicines when they are prescribed corticosteroids; others not on insulin may require insulin to manage fasting and/or postprandial hyperglycemia and the related symptoms. The choice of GLM depends on the person's health status, corticosteroid regimen, and relevant medicine precautions and contraindications [61]. Target blood glucose range is fasting ~6 mmol/l and postprandial <11 mmol/l [23, 24, 32].

Large doses of corticosteroid for more than 2 weeks can induce adrenal insufficiency, which dramatically reduces insulin requirements. Likewise, stopping corticosteroids suddenly can precipitate an adrenal crisis [64]. The signs of adrenal insufficiency are similar to other palliative care symptoms: increased fatigue, weight loss, nausea, and diarrhea [64].

33.16 Supporting family/carers

The family as a unit of care is the basic tenet of palliative care [10, 39]. Families value good communication and information about how to recognize impending death. They regard being able to advocate for their relatives, being listened to, and receiving care from services and health professionals they trust as important. These factors play a significant role in their satisfaction with care [39].

Family and other carers must be informed about and in some cases involved in developing a care plan for the person with diabetes. There can differences between people with diabetes' and their families' end-of-life beliefs and expectations. Likewise, individual family members and health professionals' beliefs and expectations can also differ.

Some family/carers may require education about how to undertake diabetes self-care tasks such as blood glucose monitoring and administering insulin to enable them to support the person with diabetes [65, 66]. It can be very stressful witnessing a loved one suffering, thus it is essential to consider carers' health status and wellbeing, including after their loved one dies [39, 67, 68]. Significantly, caring is associated with increased risk of myocardial infarction in the months after a loved one dies [69]. Research also suggests carers over age 65 are at risk of immune-related risks such as infection in the 12 months following a loved one's death due to stress-related cortisol production in the face of low dehydroepiandrosterone (DHEA) [70]. Younger carers also suffer depression and increased cortisol levels but have normal compensatory DHEA levels, which significantly reduces their risk of dying [70].

Significantly, the severity of the individual's distress is the strongest predictor of end-of-life family/carer distress [71]. Men are less likely to report caregiver strain

than women and use fewer words to describe their distress. Emotional stress is especially high in family members aged 15–25 when their family member (especially fathers) is dying from cancer [72]. Family functioning has a significant impact on the way the young person copes with the situation. They appreciate being told the truth rather than being protected from bad news. If communication is not honest they may blame themselves, imagine the worst, and/or make incorrect assumptions about the care their loved one receives and the likely prognosis.

Detecting signs of stress using clinical observation and appropriate probing questions is essential. Tools such as the Caregiver Strain Index [73] might be useful to monitor family stress. The Caregiver Strain Index is used in a variety of different disease states and in different countries to screen for carer strain in long-term caring relationships and can be used with carers of any age. The Carer Strain Index is valid (alphas range from 0.86–0.91) and reliable on test–retest (coefficient is 0.88) [73]. A positive response (seven or more items scoring positive) indicates the need to undertake in-depth assessment and follow up.

Involving family in palliative/end-of-life care can give them a sense of purpose, for example helping with feeds, providing CAM and other treatment, and scheduling rounds to coincide with family/carer visits if possible.

33.17 Advanced care plans and withdrawing treatment

Withdrawing treatment often creates ethical dilemmas. Such decisions are more difficult when people's desired end-of-life care about withdrawing or not instigating treatment is not discussed and clearly documented, and people with diabetes' preferences are not known. Health professionals should discuss treatment withdrawal with people with diabetes and their family members in a sensitive way and inform them that they have the right to stop treatment when it is no longer beneficial and when it becomes burdensome [9, 10]. It is essential to ask the person with diabetes what they want to achieve and which aspects of care they regard as burdensome and no longer useful. Many people with diabetes want blood glucose testing and glucose-lowering medicines continued until the terminal stage because testing is a familiar routine in a changing world and GLMs contribute to comfort by preventing hyperglycemia [66].

Proactively discussing end-of-life care with people with diabetes and their families in the stable stage and clearly documenting and communicating the information to the care team is essential to effective end-of-life care. However, the decisions people make when they are relatively well may change at a later date, consequently the end-of-life plan should be reassessed, for example during the annual health check and during periods of unstable disease. Box 33.2 outlines some key elements of advanced care planning.

The deteriorating and terminal phases are often key decision points for withdrawing treatment. Most people with diabetes do not want unnecessary treatment continued in the terminal phase but they want to be comfortable and die with dignity [10, 65–67].

Knowing the prognosis helps health professionals, people with diabetes, and their carers make decisions about withdrawing treatment. It is difficult to predict prognosis and some prognostic indicators were discussed earlier in the chapter. The will to live is a strong predictor of survival in older people regardless of their age, gender, and co-morbidities [74]. Social factors such as satisfaction and support from family, friends, and health professionals are important to the will to live.

Glucose-lowering medicines should be stopped when risks outweigh the benefits, for example they cause frequent, severe hypoglycemia, and other associated risks such as falls, especially in the deteriorating and terminal phases. However, the discomfort and risks associated with hyperglycemia need to be considered in light of the likely prognosis.

33.18 Diabetes education

Health professionals have a key role in enhancing coping, promoting empowerment, and supporting the individual and their families to undertake self-care, manage stress, and use health resources appropriately and effectively [10]. In addition, the reading skills and the use of unfamiliar language and concepts in many advanced care planning documents mean people often need help to understand the information in order to decide their care preferences [39]. Education and support, including bereavement support, are essential for individuals with diabetes, their families, and often health professional carers.

Sensitive discussion about the need to adjust medicines and other changes to established self-management routines is essential. In addition, diabetes educators, diabetes specialists, and general practitioners are in an ideal position to take opportunities during consultations to begin discussing palliative care and other end-of-life issues, for example during annual complication screening programs and when a life-threatening complication such as a myocardial infarction occurs, yet, as indicated, many are reluctant to engage in such discussions.

However, there is limited evidence about how often such discussion actually occurs or what factors facilitate or inhibit such discussion. Many health professionals are not comfortable discussing emotive issues such as death and/or do not want to distress patients by raising such issues. The current focus on respecting patient choice initiatives, which include planning end-of-life care and the recent publication of the Diabetes UK [23] and Dunning *et al.* [24] end-of-life guidelines may lead to change in the future.

33.19 Spiritual needs

It is essential that the care plan encompass spiritual needs and make provision to assist the individual and their families find meaning and purpose in the end of life and ensure the individual has a peaceful, dignified death. It is essential that health professionals realize that personal growth can occur up to the moment of death and that spirituality does not necessarily involve religion [75, 76]. However, religious and cultural care of the body after death should be known and in some cases documented in the care plan.

33.20 Summary

Key palliative and end-of-life care issues are presented at the beginning of the chapter and highlight significant care issues for people with diabetes at the end of life. Essentially, end-of-life care should be individualized, holistic, and encompass early detection, risk assessment, and risk management strategies to support comfort and quality of life relevant to the end-of-life stage and life expectancy. Care will differ among the end-of-life stages (stable, unstable, deteriorating, and terminal), depending on the individual's health status and especially their care preferences.

Wherever possible, the individual and their family carers should be involved in planning care such as when to withdraw treatment. People with diabetes should be encouraged to document their palliative and end-of-life care preferences while they are well enough to make such decisions.

Quality of end-of-life care requires open communication, continuity of care providers, preparing families for impending death and the signs and symptoms to look for, and especially respecting the person's choices.

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SECTION E

Optimizing diabetes care in older people

CHAPTER 34
Diabetes education and the older adult

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KEY MESSAGES

- Diabetes education is a key component of care for older adults.
- To maximize the health and quality of life of this heterogenous group, the education assessment and plan should be individualized based on the older adults' phase of living with diabetes, cognitive and functional status, co-morbidity burden, and the social and family support they receive.
- Four periods through the course of the illness that can impact how a person manages and copes with diabetes are described.
- The factors that are important for educational assessment to ensure that education appropriately addresses patient needs and the unique challenges faced by the older population are reviewed and some strategies are provided for addressing them.
- The few diabetes education interventions validated for older adults and how these interventions impact glycemic control or diabetes self-management are reviewed.

34.1 Introduction

Diabetes education is the process of helping people with diabetes and their families find and learn how to use information and skills to understand their treatment and integrate diabetes management into their lives. Diabetes education focuses on self-care with the goal of maximizing health and quality of life while preventing complications and minimizing costs. Thus, diabetes education is much more than the provision of information: it is an important component of care for all people with diabetes [1]. Ongoing and repeated education is necessary to help people update and reinforce what they learned during the initial education [2]. Formal diabetes education improves diabetes self-care and glycemia [1, 3], particularly when a behavioral intervention is incorporated. Furthermore, the Diabetes Control and Complications Trial established the importance of diabetes educators in supporting patients' efforts to manage diabetes [4]. Despite the key role diabetes education plays in self-management and adherence to diabetes treatment prescriptions, little is known about the best education strategies and interventions to use for older adults [5]. Thus, an important first step of successful diabetes education for older adults is understanding and addressing changes in physical, cognitive, psychological, and social domains and how these changes impact diabetes self-care [6].

34.2 Phases of living with diabetes

Living with a chronic illness can have serious psychosocial implications for individuals of any age. The psychological response influences how that person implements diabetes self-care and the support they need during the education process. These responses follow a general progression of four distinct phases

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from the time of diagnosis until complications are so dominant that they may overshadow diabetes care [7, 8], but individual responses within each phase vary depending on circumstances, family support, and health status.

34.2.1 Diagnosis

On diagnosis, the person must shift their self-identity from that of a healthy person to that of someone with a serious chronic illness with rigorous self-care requirements [9] and the risk of devastating acute and chronic complications [10]. This diagnosis is often accompanied by feelings of being stigmatized, particularly if insulin is used, feeling blamed, or experiencing self-blame [11]. Older people have spent many years developing habits and lifestyle patterns that may conflict with diabetes prescriptions and treatment recommendations. The onset of diabetes may differ for those with type 1 versus type 2. Type 1 diabetes onset is less common among adults over 65 and may occur as latent autoimmune diabetes of the adult (LADA), which can mimic type 2 diabetes [12]. The onset of type 1 can be abrupt, a crisis that requires rapid learning of survival skills, sometimes while hospitalized. For those with type 2, the onset may be slower, more insidious. In fact, type 2 diabetes may be considered a normal part of aging, particularly if other family members or friends have diabetes, while others may find diabetes to be catastrophic or a sign of failure. Those with type 2 may face changes in lifelong habits around food and physical activity. In both situations, the individual needs to rapidly acquire information and adapt to demanding prescriptions and self-care regimens. The diagnosis of diabetes may be so overwhelming that it prevents retention of self-care, treatment, and health information. These responses coupled with cognitive declines and physical disabilities often associated with aging make coping with the initial diagnosis of diabetes in the elderly particularly challenging.

34.2.2 Health maintenance/prevention phase

Once people become less overwhelmed and more familiar with living with diabetes, they enter the second phase, the health maintenance and prevention phase, where most people with diabetes reside. Treatment and education during this phase focuses on prevention of diabetes complications through abandoning unhealthy lifestyles and developing new habits to promote health. However, the patient may lack motivation for lifestyle adjustments, particularly for individuals whose coping styles include procrastination and denial.

Many people put diabetes on the "back burner" when competing demands and priorities predominate, and diabetes may be assigned a lower priority in their lives. Family members of older adults through concern and worry may attempt to regulate their relatives' behaviors, especially food choices. This situation may place an undue burden on family relationships that may benefit from intervention by healthcare professionals. Furthermore, if older individuals feel lonely or isolated and develop elevated depressive symptoms or increased distress, they may be unable to implement the diabetes self-management that is necessary to maintain health. Conversely, a recent study found shown that older individuals in poor glycemic control, aged 60–75 years, benefited more from diabetes education interventions than those who were middle-aged [13].

34.2.3 Onset of early complications

Onset of early complications begins a new disease trajectory. Patients may suddenly realize they are at serious risk of losing important abilities through complications or co-morbidities. Some older adults respond to the early diagnosis of complications by becoming energized; the diagnosis then serves as a wake-up call to start managing their diabetes better. Others may respond with a sense of fatalism and increased distress and/or isolation. They may become incapacitated and unable to manage their diabetes. Each person may require a different type of support and education to cope and to maximize health and quality of life. Furthermore, as older adults become sicker with diminishing executive functions, their treatment regimens, particularly their medication, may become so complex that they are unable to follow their prescriptions accurately and safely. Subtle cognitive decline may be difficult to detect and thus may require a specialized assessment [14]. Healthcare providers should take care not to inadvertently reinforce self-blame or use terms that could be interpreted as blaming and/or shaming [11]. Behavioral and emotional support for both elderly patients and their caregivers can be useful to help address negative

attitudes and perceptions that interfere with self-care and quality of life.

34.2.4 Complications dominate

When complications dominate, diabetes often becomes a lower priority and people may start to focus on co-morbidities or complications that require more care, are perceived as more serious, or cause more pain [15]. The patient can be faced with several different illnesses with which to cope instead of focusing on one diabetes treatment program. Thus they may have a new team of healthcare providers and their efforts may shift away from diabetes. The treatment plan becomes even more complex and often the older patient requires professional support, even assisted living or nursing home placement, to implement prescriptions appropriately.

34.3 Educational assessment of factors associated with diabetes self-care

A thorough education assessment is necessary for appropriately individualizing diabetes education and training that is based on the older person's current health, self-care, and cognitive status. This assessment may need to be repeated at least yearly or upon major changes in treatment or health status and cognition. Table 34.1 summarizes important assessment areas.

34.3.1 Clinical and functional factors

Diabetes education necessitates special attention to older adults' clinical and functional changes. Age-related decreases in muscle mass, aerobic capacity,

Table 34.1 Important areas to consider in the educational assessment.

Assessment area	Key assessments	Comments
Self-care skills	Specific skills: how insulin is injected, how pen is used	Have patient demonstrate how they do tasks so their technique can be evaluated
Self-care knowledge and Information	Understanding of self-care recommendations	Have person describe what he/she does to care for diabetes instead of responding to yes/no questions
Cognitive status	Confusion, dementia Subtle changes in executive functions	Mini-mental for dementia Clock in the box task Subtle executive deficits are difficult to assess/detect
Literacy and health literacy	Assess ability to read and understanding of prescriptions and ability to follow health directions Assess in which languages patients read	Visual problems can impede one's ability to read, have magnifiers available Illiteracy can be embarrassing; it should not be equated with intelligence Speaking a language does not equate to reading in that language
Social support	Frequency of contact with family, friends Quality of social support Community or religious group involvement Participation in social activities	Lack of social interactions can impact both nutrition and mobility. Families may provide negative support that could serve to impede self-care
Psychosocial issues	Depression is more common among both those with diabetes and the elderly Diabetes-related emotional distress is more common than depression and is related to glycemia and living with diabetes	Although responsive to medications, depression is both under-recognized and under-treated Psychological counseling can help with both conditions
Culture, attitudes and beliefs	Assess how important diabetes self-care is for that person and what the patient's health priorities are	If patients' priorities differ from providers, both communication and diabetes management may be negatively impacted
Physical status and functionality	Hearing, visual and other sensory impairments Complications and co-morbidities	Pain and limited movement may have a higher priority for patients than diabetes management

visual and auditory acuity, bone strength, and joint flexibility contribute to physical, functional, and cognitive decline [16], which can lead to disability [17], impairment of activities of daily living [18], poor perceived health [19], and lower quality of life [20]. Risk for falls and fractures, and subsequent functional limitations are associated with high rates of peripheral neuropathy, skeletal muscle loss associated with undernutrition, and hypoglycemia [21–23]. Furthermore, older adults' functional limitations can change over time and are related to increased hospitalizations [24]. Thus, older adults' clinical and functional changes can have a deleterious impact on diabetes self-care [25], health status, and quality of life [26], and pose competing demands that require substantial time, effort, and money to manage effectively [27].

For the elderly, diabetes education focuses on the clinical and functional changes associated with aging and diabetes. Educators should assess and address the negative impact these changes have on diabetes self-care and glycemia, and also consider older adults' values and preferences for care [28]. Most older adults have some diminished sensory perception. Specifically, older adults with diabetes are more likely to suffer from glaucoma, cataracts, and retinopathy (i.e., nonproliferative retinopathy, macular edema, proliferative retinopathy) [29]. Also, they are more likely to experience hearing loss [30], nerve loss and subsequent loss of sensation [31], and altered taste and smell perception [5]. Thus, diabetes education should address sensory changes in the content and delivery of information, and be delivered in easily accessible locations with appropriate sensory aids (Table 34.2).

34.3.2 Co-morbidity and complications

As individuals age, the number of health conditions increases, with four out of five adults aged 65–74 years and five out of six adults aged 75 and older diagnosed with at least one co-morbid condition in addition to diabetes [32]. On average, older adults with diabetes have approximately 3.5 other chronic conditions [33]. The most common co-morbid conditions include obesity, hypertension, dyslipidemia, arthritis, hearing impairment, obstructive sleep apnea, fatty liver disease, periodontal disease, and certain cancers [32]. Furthermore, older adults with diabetes are at increased risk for macrovascular (i.e., cardiovascular disease) [34] and microvascular complications (i.e., retinopathy, nephropathy, neuropathy) [35] as well as geriatric syndromes, including depression, cognitive impairment, injurious falls, neuropathic pain, and urinary incontinence [5]. Co-morbidities and diabetes complications can have a negative impact on older adults' diabetes self-care [25, 36], health status, and quality of life [26].

High rates of co-morbidity and diabetes complications among older adults with diabetes warrant attention in diabetes education. Co-morbidities and diabetes complications may pose competing demands that require substantial time, effort, and money to manage effectively [37]. However, complications and co-morbidities may have differential impacts on older adults' diabetes self-care. Some older adults may perceive certain conditions as more serious than diabetes and selectively attend to the self-care of those conditions based on this perceived severity or importance [15]. They also may not understand the relationship between clinical and functional changes, and diabetes progression. For example, older adults may not know that improving glycemic control can reduce neuropathic symptoms [38]. Thus, the educator's role is to help patients understand the interconnection of their various conditions and the impact of frequent and appropriate self-care on their overall health, glycemia, and quality of life.

34.3.3 Polypharmacy

Because of their high co-morbidity burden, older adults with diabetes are at high risk for polypharmacy, a term describing when multiple medications are prescribed for multiple conditions [39]. Although a standard definition does not exist, most define polypharmacy as taking five or six medications per day [40]. In one study, older adults with diabetes reported taking 8.2 ± 4.0 medications each day [41]. These may not include over-the-counter, herbal, or medications such as acetaminophen that may be taken on an "as needed" basis, therefore self-report may underestimate the actual number of medications taken. Higher numbers of daily medications increase the complexity of medication self-management, the overall and out-of-pocket costs, and the risks of medication error and poor adherence [42]. Further complicating the issue is that medications are often prescribed by different practitioners and may be filled at different pharmacies, making duplication and potential interactions difficult to identify.

Older individuals are at increased risk for adverse drug effects secondary to age-related changes in

Table 34.2 Tips and strategies to accommodate sensory loss in diabetes education.

Sensory loss	Comments
Vision loss	Make sure the education room provides a good source of light without shadows or glare. Sit or stand where older adults can see you. Remove cords, chairs, or other objects from areas where older adults have to walk. If you darken the room to show slides or videos, give older adults a couple of minutes to adjust their eyes to less light in the room. If you provide education materials, make sure the font is large with black print on matte white paper. Sentences should be brief and not in all capital letters. Encourage older adults to use eyeglasses and/or large magnifiers during the education session. Have one or two large magnifiers in the education room for older adults with vision loss.
Hearing loss	Speak clearly and distinctly using a normal tone of voice. Do not shout when speaking to older adults. Talk face-to-face so that the person can see your lips. Older adults with hearing loss often support their hearing with lip reading. Avoid writing on a whiteboard and talking while your back is to older adults. Do not chew gum or cover your month when speaking. Use a microphone if you are speaking to a group. Stand still when talking to older adults. Avoid pacing in the education room because older adults may have difficulty reading your lips. Select an education room with reduced background noises (e.g., fans, heating vents, television, etc.). Use visuals that reinforce your spoken word. Make sure the visuals are in large font printed in black on white matte paper or white background slides. Repeat questions from older adults before answering the question to demonstrate that you understood the question and to allow others in the group to hear the question again. Allow adequate time for older adults to respond to questions you ask as they make take longer to process information and respond.
Poor sense of touch	If you are demonstrating a self-care behavior that requires touch, explain what you are doing before touching the older adult. Increase the pressure when touching the older adult, without causing pain.
Loss of taste	When discussing nutrition education, include information or visuals of foods that look appealing. Encourage older adults to vary the texture and flavors of the foods they prepare and to separate foods on their plate. Emphasize the importance of good oral hygiene, including cleansing tongue prior to eating. Remind older adults to stay hydrated by drinking plenty of water with meals. Recommend Increased the use of spices (not salt) to stimulate taste.
Loss of smell	Encourage older adults to label foods that look or smell similarly. Food should be visually appealing and textually interesting to stimulate appetite.

pharmacokinetics, notably changes in renal function. Furthermore, the risk for drug interactions is also higher. In a review of 17 studies of potentially harmful drug interactions in the elderly, Hines [43] reported a variety of drug–drug interactions that often required hospitalization with the interaction between sulfonylureas and antimicrobial agents being among the more frequently occurring interactions.

Two diabetes medications meet the Beers criteria [44] as potentially inappropriate for vulnerable older adults: sliding-scale insulin and long-duration sulfonylureas (chlorpropamide and glyburide) due to their higher risk of hypoglycemia in the elderly. Older patients need to understand symptoms of and how to respond to and prevent hypoglycemia. Importantly, they are at risk of nocturnal hypoglycemia and therefore falls [41].

34.3.4 Psychological factors

Older adults with diabetes experience disproportionately high rates of depression, diabetes distress, and other emotional difficulties [45–47]. An estimated 14–28% of older adults with diabetes have depression [48, 49], which is two to four times higher than that the general population aged 65 and older [50]. Depression interferes with self-care [51, 52] and worsens glycemic control [52]. Furthermore, depression is associated with

microvascular and macrovascular complications (e.g., retinopathy, neuropathy, nephropathy cardiovascular disease, hypertension, and sexual dysfunction [53, 54]), physical limitations [55], increased hospitalization, and mortality [56]. Thus, diagnosis and treatment of depression is critical to improve self-care and glycemia, and to reduce morbidity and mortality in older adults with diabetes. Importantly, older adults may present with different cognitive, physical, affective, and attitudinal symptoms than the typical depressive symptoms observed in younger adults [57]. Moreover, physical and cognitive symptoms may overlap with hyperglycemia, which can complicate the diagnosis of depression in older adults with diabetes [58].

Diabetes distress is a common condition distinct from depression as it develops from living with diabetes [47]. Diabetes distress includes frustration with self-care, concerns about the future and the possibility of developing complications, worries about the quality of medical care and the cost of that care, and perceived lack of support from family members and/or friends [59]. Diabetes distress is actually more common than depression in individuals with diabetes, with a prevalence of 18–35% [60, 61]. Similar to depression, diabetes distress is associated with poor glycemic control [59, 61], reduced self-care [62], and increased morbidity [63]. What remains unknown is whether rates of diabetes distress are higher in the older population. For this reason, an improved understanding of the frequency and seriousness of diabetes distress in this patient population is needed.

Diabetes education for older adults should include information about depression and diabetes distress. Particular attention should be paid to distinguishing depression and diabetes distress as well as typical and atypical depressive symptoms in older adults. Discussion about depression and distress may reduce stigma and address the misconception that these conditions are normal parts of the aging and/or diabetes processes. Also, diabetes education should emphasize the importance of communicating symptoms of depression and diabetes distress to healthcare providers. Older adults may be reluctant to communicate symptoms due to financial or medication concerns [64, 65], prioritization of co-morbid conditions [15], or lack of a support system [66]. Open communication with healthcare providers may improve diagnosis and treatment and, in turn, improve self-care and glycemia.

34.3.5 Social factors

Diabetes requires complex self-care prescriptions, including weight reduction, increased physical activity, diabetes nutrition guidelines, oral and/or insulin medication regimens, and frequent blood glucose monitoring. The majority of self-care is performed at home [67], therefore diabetes and its demands can be influenced by family members [68]. Thus, social support, particularly family support, is an important factor in the successful management of diabetes. Social relationships benefit individuals with diabetes via social support (e.g., emotional, instrumental, appraisal, and informational), social influence (e.g., shared norms around health behaviors), social engagement (e.g., definition and reinforcement of social roles and participation), and access to resources (e.g., goods, services, and opportunities) [69]. Social support is associated with improved self-care, glycemia, and other health outcomes [70, 71]. Strategies for improving self-care should promote social support, social influence, social engagement, and access to resources.

Existing diabetes education tends to focus on individuals making behavioral changes, yet few individuals make these changes in a vacuum. Family members and friends play key roles in helping or hindering behavioral change. Older adults with diabetes may benefit more from social support because of physical limitations, co-morbid conditions, visual and/or hearing impairments, lack of resources (e.g., transportation, finances), retirement, loss of family members and friends, loneliness, isolation, and fears about mortality. Diabetes education designed to enhance older adults' capabilities as well as family members and/or friends' support may improve self-care and glycemia. Diabetes education can be offered to older adults with their family members and/or friends at convenient settings (e.g., worksites, recreational facilities). Also, diabetes education for older adults can include learning contracts with family members and/or friends to set collective goals and establish effective strategies for achieving them. Lastly, diabetes educators and other providers can work with older adults and family members and/or friends to assess their collective experience with self-care and monitor their progress as a unit.

34.3.6 Cognitive function

Older age and diabetes are independent risk factors for cognitive function impairment; the presence of both factors increases this risk [72]. Cognitive impairment

ranges in severity from mild cognitive impairment to severe dementia. Often mild cognitive impairment is unrecognized by patients and providers [5]. Although an individual with mild cognitive impairment may be able to engage in daily life activities, problems with memory may be greater than normal. In the most severe forms of dementia, the individual loses the ability to think, remember, and reason, and therefore is no longer able to carry out usual activities such as bathing or dressing independently [73]. Evidence from several observational studies has consistently demonstrated the independent association of type 2 diabetes and cognitive decline increased risk for dementia [74, 75]. Type 2 diabetes is related to not only vascular dementia but also Alzheimer's disease [76]. Of note, early signs of cognitive decline may already be present at diagnosis of type 2 diabetes. In one population-based cohort study [77], controlling for intelligence scores, memory performance was significantly reduced for individuals newly diagnosed with diabetes compared to those without diabetes; those who had a history of macrovascular disease and smoking were more likely to be affected.

Even in those with perceived normal cognition, diabetes may be associated with poorer executive function [78]. Executive functions are higher-level cognitive operations, including the ability to problem solve, plan, and organize, tasks that are essential to diabetes self-care. Memory is an important component of executive function. Poor cognitive function impairs one's ability to perform many self-care tasks, particularly those that rely on numeracy, such as interpretation of blood glucose values, changing insulin doses, drawing an insulin dose into a syringe or dialing a dose for insulin administration via an insulin pen [5]. Thus, cognitive function is an important component of the educational assessment and subsequent approach for the older adult living with diabetes.

As the risk of cognitive impairment in older adults with diabetes is high and early changes in cognitive function may be subtle, periodic assessment is needed. Although a wide range of instruments to assess cognitive impairment is available, assessment measures must be valid, reliable, easy to administer, and brief to be useful in the education setting. Lin and colleagues [79] conducted a systematic review to examine the test performance of screening instruments to detect cognitive impairment. Of the instruments identified, five were categorized as being very brief (≤5 min). Of these, the Clock Drawing Test takes approximately 2 min to complete, has good internal consistency and reliability [80], and correlated well with the longer Mini Mental State Examination (8–13 min) in older adults with diabetes [81]. However, neither test is sensitive to the subtle changes in executive function that occur with normal aging.

Diabetes education and treatment goals must be tailored to the needs of the older adult. Healthy older adults receive similar glycemic benefit from participating in group diabetes education classes compared to younger adults [13] and should be encouraged to do so whenever possible. However, glycemic goals for adults with mild or more severe cognitive dysfunction often need to be adjusted to prevent recurrent or severe hypoglycemia and undue treatment burden [5], and treatment regimens simplified. Caregivers, when available, should be encouraged to participate in diabetes education whenever possible so that self-management of the older adult with cognitive dysfunction can be optimized.

34.3.7 Health literacy

Understanding health instructions can be challenging for many. Approximately one-third of Americans have basic or below basic literacy skills and poor math skills [82]. Low health literacy is more common among older adults as well as those with lower education, immigrants or those from racial or ethnic minority groups [83]. Health literacy is key to an individual's ability to acquire, process, and understand health information in order to make appropriate decisions to support their health [84], and requires reading and writing skills to interpret printed information, speaking and listening skills to effectively communicate, and numeracy skills [85].

Diabetes self-care relies on literacy and numeracy skills. In a sample of 398 adults with type 1 and type 2 diabetes [86], less than half were able to accurately calculate the total grams of carbohydrate in a container of snack chips or calculate an insulin dose adjusted for blood glucose level and carbohydrate intake. Furthermore, less than two-thirds were able to draw up a specified amount of insulin into a 100 unit syringe, or estimate the date when they would run out of test strips. Clearly, these are not unusual daily tasks for people living with diabetes. However, an individual's health literacy may not always be readily apparent to health

Table 34.3 Low literacy diabetes education resources.

Name	Developer	Description	Website
Diabetes Literacy and Numeracy Education Toolkit (DLNET)	Center for Diabetes Translation Research, Vanderbilt University School of Medicine	24 education modules Available in English	http://www.mc.vanderbilt.edu/documents/CDTR/files/ddlnet-toolkit.pdf
Living with Diabetes	American College of Physicians	56-page booklet Developed by diabetes educators, physicians, nurses, and patients Six focus areas relating to nutrition, physical activity, blood glucose monitoring, medications, foot care, and insulin Available in English, Spanish, and Chinese	http://www.acponline.org/patients_families/products/brochures/

professionals and may impair the quality of patient–provider communication surrounding health, therefore negatively impacting the quality of the patient–provider relationship [87]. Furthermore, patients with low health literacy often attempt to conceal their limitations because of shame.

A recently updated systematic review examined the relationship between low health literacy and health outcomes [88]; of 96 cohort and/or cross-sectional studies included in the review, 15 involved diabetes or the elderly. The findings of the systematic review demonstrate that patients with low health literacy have difficulty with healthcare skills such as taking medications appropriately (moderate evidence) and had poorer health status (moderate evidence) and higher all-cause mortality (high-quality evidence). Therefore, it is essential that diabetes educators routinely incorporate strategies into their everyday encounters with individuals with diabetes to maximize the benefit of diabetes education for those with poor health literacy.

Although a number of rapid screening tests are available to effectively assess health literacy, their routine use for educational encounters in the clinical setting may have the unintended consequence of stigmatizing and alienating patients [89]. However, patients who have difficulty with reading or math may provide clues to their literacy status by behaviors such as saying "I forgot to bring my glasses" when asked to read or fill out a form. Health professionals should take universal precautions when delivering diabetes and other health education not only to older adults, but to all requiring diabetes education as if every patient may have limited health literacy. The Centers for Disease Control and Prevention created a guide, *Simply Put* [90], for developing easily understood health materials. These guidelines address strategies for making messages clear, using visuals to convey messages, options for layout and design, including text appearance, and attention to cultural considerations. In addition, the guide includes instructions for the Simple Measure of Gobbledygook (SMOG) [91], Fry [92], and other methods for calculating the reading levels of educational materials. All health education materials should be written at a fifth- to sixth-grade reading level or lower [93]. In addition to using only education materials that meet low literacy guidelines, educators should employ teach-back strategies where patients restate in their own words their understanding of what has been communicated to them. This technique provides an opportunity for educators or clinicians to assess patient comprehension and correct misperceptions. Table 34.3 lists diabetes education resources that meet low-literacy guidelines.

34.4 Diabetes educational and behavioral support interventions

Although many randomized controlled trials exclude those over 65 years of age, the Consensus report on Diabetes in the Older Adults [5] highlighted the paucity of clinical evidence available to guide clinicians in behavioral and education intervention approaches. Some evidence is now emerging that those up to at least age 75 years (some older) benefit either more or the same as middle-aged and younger adults [13, 31, 94]. Other diabetes education and behavioral intervention studies

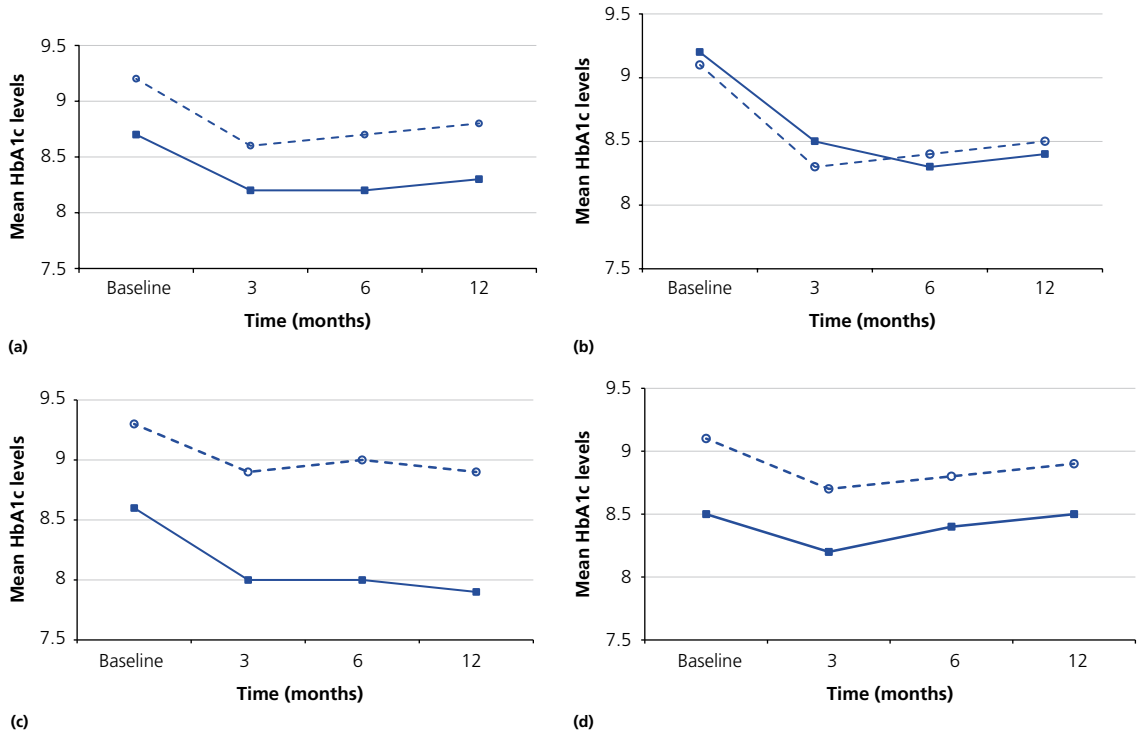

Figure 34.1 Mean HbA1c levels over time for older versus middle-aged adults participating in randomized controlled diabetes education study: (a) all participants, (b) structured cognitive behavioral intervention group education, (c) standard group education (attention control), (d) individual education (control). White circles, younger adults; black squares, older adults. Reprinted with permission of the American Diabetes Association, Diabetes Care 2013; 36: 1501–6.

have included individuals up to age 87 years [95, 96] but how those aged 65–87 years benefited is not clear [97].

34.4.1 Group versus individual

Group education is looked upon as more economical and thus becoming more popular in health over the past few decades [98, 99]. Many providers are reluctant to recommend group educational and behavioral interventions for older individuals as conventional wisdom suggests that older adults benefit from individualized attention from educators. Few well-done studies have directly compared group versus individual educational interventions [100]. One study examining middle-aged adults found outcomes to be comparable except for better glycemic control after 6 months in the group education arm [101]. One randomized controlled trial that did a subgroup analysis of the impact of the intervention on the older adult found that those between 60 and 75 years of age who were cognitively intact had a greater glycemic improvement when participating in group education than individual education [13] (see Figure 34.1).

34.4.2 Goal setting

There are two types of goals in diabetes care. One type includes the medical goals or targets used to determine treatment effectiveness. HbA1c, a measure of average glycemia over the prior 2–3 months, is a typical factor for which targets are set. HbA1c results are tracked and used as the basis for changing medications or approaches. Other typical medical goals may address lipids, renal function, etc. Patients, on the other hand, may use self-care goals to direct or improve their diabetes management skills. These self-care goals are a common behavioral technique recommended by educators and may address areas such as food choices, carbohydrate consumption, checking glucose levels, etc. These goals are used by patients to

Table 34.4 Steps for helping patients set self-care goals.

Goals are determined by the patient with support from the educator (RN, RD, EP, MD)	Examples
Acknowledge broad overall long-term goals	Lose weight, exercise more, etc.
Identify specific short-term goals	Lose 10 pounds over 5 months
Identify all steps necessary to reach short-term goals	**1** Eat only when sitting at the table (never when watching television). **2** Change regular soda to diet soda. **3** Drink 8 glasses of water each day. **4** Set up appointment with dietitian.
Evaluate progress towards goal, not whether or not the goal was met	How many steps were successfully achieved? Did that amount to 10%, 20%, etc. of goal?
Evaluate whether plan helped or hindered achieving goals Reset goals as necessary	

help put organization into their everyday lives. Table 34.4 lists helpful steps for setting goals.

34.4.3 Other behavioral-based diabetes education interventions

The same study mentioned earlier [13] also compared glycemic improvement between older adults aged 60–75 years compared to middle-aged adults. Older adults in the three educational interventions improved either more or the same as those who were middle-aged (Figure 34.1). The highly structured cognitive behavioral-based experimental arm included cognitive restructuring. This technique, when embedded in diabetes education, can be useful to help combat some of the negative effects displayed by diabetes patients. However, patients with major depression require further treatment with psychotherapy or medications or both. Other behavioral approaches included goal setting and planning, and specific homework addressing glucose monitoring and interpretation, which was always then addressed in the group sessions.

The multi-site 8-year LookAHEAD study [102] examined the impact of an intensive lifestyle intervention versus standard group education on obese type 2 diabetes patients. The lifestyle intervention targeted weight loss through educator facilitated healthier food choices and increased physical activity. The investigators found that older participants (aged 65–76 years at baseline, thus 73–84 years at study completion) lost more weight than middle-aged participants in both the intensive and control arms, with the intensive lifestyle arm losing more weight than controls, leading the authors to speculate that both the lifestyle intervention and aging may have played a role in the weight loss. Although increased physical exercise improves health benefits for the older adult with diabetes [31], few studies have examined the impact of increased exercise on cognition among those with diabetes, even though studies have found that exercise improves cognition in healthier older individuals [103, 104] and in older persons with pre-diabetes [105].

Motivational interviewing is a valuable counseling tool that can be embedded within an intervention but it may not be effective as a standalone intervention [106]. In fact, some evidence shows motivational interviewing, rather than enhancing, may have a deleterious influence on standard diabetes education [106]. The problem may be that educators participating in well-done randomized controlled trials follow strict protocols developed by psychologists and do not have the opportunity to adapt the interviewing techniques to their own practice patterns and areas of focus.

As the world population ages, we need evidence to help determine the best educational approaches for older adults who have been treated much of their lives with an insulin pump or intensive multiple daily injections. Use of continuous glucose monitoring has been useful in studies to identify nocturnal and other hypoglycemic events [41], but whether such tools would be an effective component of diabetes treatment for the elderly is not clear. Educational research has become more rigorous among the middle-aged adult diabetes

population but now similar rigor is required to study educational approaches for the elderly, particularly those over 70 years of age.

34.5 Summary

Diabetes education is an effective tool to support the older adult with diabetes and their families. The physical and cognitive changes associated with aging may trigger negative emotional responses. All three of these factors can impact diabetes self-care and quality of life. Fortunately, this problem is now recognized and some evidence is beginning to emerge that will help clinicians provide the quality of care necessary for successful treatment of the elderly with diabetes. Much more evidence is now needed to help direct clinicians to the appropriate interventions for the diverse population of older adults with diabetes.

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CHAPTER 35

Supporting the family and informal carers

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KEY MESSAGES

- Informal carers (caregivers) are the primary source of everyday advice, emotional support, and practical help for many older people with diabetes.
- A supportive environment for carers that enables them to receive education and advice about diabetes and its management, and creates opportunities for them to be involved in treatment decisions is essential.
- The physical, emotional, social, and economic effects of caring on the health and wellbeing of the carer must be assessed regularly.
- Some experts recommend the care recipient–carer dyad be managed together.

35.1 Introduction

Most older people with diabetes live at home, often with support from family and friends. Many of these people would not regard themselves as requiring care, and most close relatives would not regard themselves as carers. Nevertheless, many older people with diabetes around the world seek advice as well as practical and emotional support to manage their diabetes and its complications, and to adopt and maintain a healthy lifestyle from their families and sometimes their close friends.

There is a significant body of literature about the role of family carers for people with type 1 diabetes [1, 2] where health professionals assume parents will play an active role in positively influencing management and make an effort to ensure glucose control is optimal. Numerous studies examined the value of psycho-educational interventions and family support on the health outcomes of children and young people with type 1 diabetes and show family-based interventions can improve diabetes knowledge, promote adherence to management regimens, achieve better glucose control, and increase quality of life and emotional health [3, 4].

In contrast, health professionals and policy makers only recently began to acknowledge the important role family carers play in supporting their older relatives to manage their diabetes or undertake diabetes self-care on behalf of their older relative. Several guidelines and papers highlight the importance of involving family carers in care and other decisions where relevant [5]. Carers need education about how to perform various self-care tasks, recognize deterioration such as signs of diabetic emergencies, and how and when to seek health professional advice [6].

The National Institute for Health and Clinical Excellence Type 2 Diabetes Guideline [7] acknowledged that diabetes is "…predominantly managed by the person with the diabetes and/or by their carer as part of their daily life" and that, if the individual agrees, families and carers should be involved in decisions about treatment and care and be given the information and support they need to provide care.

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Structured education should be offered "…to every person with diabetes and/or their carer at and around the time of diagnosis and with reinforcement and review on an annual basis" [7, 8]. The average person with diabetes spends approximately 3 h a year with a health professional. They will undertake diabetes self-care for the remaining 8757 h. Family carers manage a range of complex issues such as:

- cognitive changes due to dementia or hyper- and hypoglycemia
- activities of daily living (ADL)
- changed health literacy and learning style
- depression
- incontinence
- falls risk and actual falls
- behavior changes that can be related to dementia and/or hypoglycemia and can lead to aggressive behaviors
- assisting with medicine management
- providing transport
- palliative and end-of-life care
- financial issues [9].

Thus, family carers often assume a significant burden of care. "Family burden" is a concept adopted to identify the objective and subjective difficulties carers experience when providing care for a family member. Caring can disrupt relationships and lead to constraints on work and leisure time, can be a financial burden, and can have a negative impact on the carer's health and quality of life. "Subjective burden" encompasses psychological reactions such as grief, anger, and loss that can lead to hostility and anger, which can result in elder abuse [10]. Therefore, it is important that health professionals and health services ensure they provide or help carers access the information and resources they need to care.

In practice, families and other non-professionals are involved in various aspects of care of older people with diabetes. For example, an observational study of people aged ≥70 years participating in a study of type 2 diabetes in primary care found between 22% and 50% of participants' family members reported helping with various aspects of diabetes care [11]. Likewise, most older people attending hospital-based diabetes clinics reported they regularly received help with day-to-day activities and/or other care [11]. Approximately 50% of older people are on insulin [12]. Thus, family carers are a significant source of support for older people with diabetes [12–14]. However, service providers often do not consider carers' needs because they focus on the needs of the care recipient.

35.2 Who are carers?

Informal carers are invaluable to the care of older people with diabetes [9]. Most of the care provided by family carers is hidden from clinicians. The average age of carers is 63 and over 30% of carers are in poor health themselves [15]. Most carers are women but more than 40% of carers are men [16]. Most carers are spouses but siblings, children, friends, neighbors, or members of a specific support system such as a church or social organization also provide care. Women carers generally outnumber men carers, but more men than women over age 85 are carers in the UK [17]. Men are reported to take a more task-based approach to caring than women carers, who tend to use emotion-focused coping strategies and report higher levels of distress and poorer health than men [18].

The results of the carers module of the General Household Survey in the UK in 2000 [19] reported that 52% of carers were caring for a parent or parent-in-law and 18% were caring for their spouse or partner. Two-thirds were caring for women, which is consistent with the predominance of women in the older age groups. The most common age group of carers was between 45 and 64 years (24%); although 12% were over 65 years. Whilst some reports focus specifically on the informal carers of older people with diabetes; most reports concern the broader carer literature [11, 20, 21].

Generally, one person takes the lead carer role, and may or may not have a secondary network of support from other relatives and friends. The role of primary carer is often undertaken by a partner, husband or wife. Wives provide most care followed by daughters, daughters-in-law, granddaughters, and sons. Other factors such as living with or closest to the older person, competing responsibilities such as employment, childcare, and other family responsibilities influence family members' capacity to provide care. Widowhood becomes more common with increasing age; consequently, children often become more actively involved. Husbands rarely give direct help to wives who are caring for an older relative and women are more likely to give up their job to take on caring responsibilities [22, 23].

It is fairly clear that there is often a "caregiving trajectory" where the nature of caregiving varies over time [24] for most adults. This may be especially true in poorer communities where three caring phases have been identified: semi-care, care, and end-of-life care.

Ethnicity also plays an important role, with differences in the caring roles and expectations [25]. Due to patterns of migration, there are proportionally more older men requiring care within ethnic minorities and there is less acceptability of available formal care services and institutional care. Consequently, there is a greater care burden on families.

Godfrey and Townsend [26] found that caring is influenced by gender role stereotypes and filial responsibility. Spouse carers were less common and carers tended to be younger [27]. Sons took a more active responsibility for decision making, organizing care, and assisting with instrumental activities of daily living, with daughters and daughters-in-law helping with personal care and housework. Often, daughters and daughters-in-law did not regard themselves as carers, but the support given to their relative was considered part of normal family responsibilities. The belief that ethnic minority families "look after their own" and so do not require attention is not supported by evidence [28].

In many instances, adults within ethnic minority groups may be both patients with diabetes and have a caring role for younger people. For instance, in a study of 109 urban midlife African American women with type 2 diabetes, 60% were grandmothers who had higher levels of diabetes-related emotional stress and worse glycemic control than those without grandmother status, and yet had higher quality of life scores than non-grandmothers [29].

The contribution of children to care should not be overlooked. In a study of child carers of adults with diabetes by Jacobson and Wood [30], one in five were looking after grandparents, having begun caring at a mean age of 11 years. Most provided care at least several times a week, ranging from calling to check on the adult or staying with them overnight, to performing glucose testing and giving medication and insulin injections. The youngest child administering insulin was aged 5 years. Nearly half of the children had no education about diabetes care, not even from the family member with diabetes.

Significantly, adults who were caregivers as children indicated providing personal care was the hardest part of caregiving and that caregiving disrupted family and school life, and compromised the time they could spend with friends [31]. Lackey *et al.*'s findings suggest it is important that children providing care have time to be children [31].

35.3 What do carers do?

The term "carer"' relates to a broad spectrum of tasks, ranging from emotional support, to organizing help, to providing company, to doing household tasks, to help with intimate personal care. Care can be provided for a short time, for example after a stay in hospital, or longer, on average 4.5 years [32]. Carers spend an average of 8 h per week providing care: range 1–40 h, especially when multiple medicines are required and several doses of medicine are prescribed per day [33].

In the General Household Survey [19], over two-thirds (71%) of carers provided practical help such as preparing a meal, shopping, and doing laundry, 60% kept an eye on the person being cared for, and 55% provided company. Smaller proportions of carers provided more intimate forms of help. About one-quarter (26%) gave assistance with personal care such as washing, 22% administered medicines, and 35% provided physical help, for example with walking (Table 35.1).

The availability of a close family member or friend to take on the role of carer, rather than need, seems to be the most important predictor of having someone involved in medical care [33], and not all recipients of care appreciate the level of involvement (too little or too much) that is provided [34].

The general carer research literature distinguishes between caring (the affective component) and caregiving (the behavioral component) [35]. "Care providers" give: hands-on care such as dressing, bathing, daily supervision, cooking, managing finances, and transportation. "Care managers"' arrange for others to provide care, for example organizing a nurse to attend daily to give medication or dress leg ulcers, a professional carer to attend to personal care and provision of meals, an accountant to manage finances, and social care assistants to provide companionship and supervision during the day.

Care providers are most often spouses (especially wives) and daughters/daughters-in-law, whilst care managers are most often husbands, adult children

Table 35.1 Overview of the care that caregivers take responsibility for delivering.

	Tasks carers undertake
Physical care	Medical and nursing care such as dressings and pain management, administering medicines, and monitoring their effects, such as blood glucose testing Observing and recognizing changes and symptoms, and interpreting their urgency and the need to seek health professional advice Assisting with activities of daily living such as bathing, managing continence, and urinary catheters Supervising self-care and meals Managing medical technology and electronic equipment. Knowing how and when to access community services and which services to access Managing behavioral problems, such as people with dementia, and the cognitive changes that can occur during hypo- or hyperglycemia Helping the individual document their end-of-life care plan
Other tasks	Navigating the health system Interacting with health professionals and others in the health system Knowing how to access equipment, products, and medicines Making decisions Managing finances Assisting with shopping and transport Attending appointments with the care recipient Responding to care recipient's "alert" calls for assistance Ensuring they take care of their own health

(especially sons), friends, and other relatives. Care providers tend to be more burdened and/or stressed than care managers, but inevitably have less contact with professionals who might be able to provide practical and emotional support [36].

Murphy *et al.* [20] undertook a study in a family practice in the USA to examine the supportive roles of family members of adults with type 2 diabetes (mean age 59 years) and identified two broad categories of family participation in care giving. As well as the conventional supportive family member (primary carer or helper) who provided supportive tasks in the care of the illness, there was often the "family health monitor", an internal health expert usually consulted before any consultation with external resources, including the doctor.

Family health monitors fulfill a unique executive function as an authoritative information resource and supervisor who critically evaluates medical advice before family members incorporate the information into daily practice. Three-quarters of the patients identified such an individual within their family, and often this was not the same person as the primary carer. No relationship was shown between the presence or absence of a family health monitor and the level of metabolic control as measured by glycosolated hemoglobin (HbA1c) level. This suggests a need for health professionals to recognize and involve family health monitors in the therapeutic team, so that they may impact more positively on management.

Murphy *et al.* also identified the most frequent helping tasks primary carers undertake. These include:

- helping the person with diabetes with their diet, including food selection and preparation ("helps buy the right foods", "cooks properly"), reminders about proper diet ("keeps after me about diet", "watches diet") and support for dietary restrictions ("cooperates at meals", "hides sugar")
- helping with medications, both general ("keeps track of medications") and specific ("buys medicine", "reads directions on medicine bottles")
- general support, defined as "encouragement" or "talking to me"
- financial support: reminders about medical appointments, assistance with hygiene and exercise.

Silliman *et al.* [11] undertook a study in primary care and found between 6% and 17% of older patients with type 2 diabetes received regular help from family

members with basic activities of daily living, and between 37% and 48% with instrumental activities of daily living. The most commonly reported help given was "keeping enough medication on hand" and "following a diet". Between 23% and 38% of family members also reported participating regularly in the patient's medical encounters, whilst 20–40% rarely or never discussed diabetes-related issues with the doctor.

When they did go to appointments, family members usually talked to the doctor with the patient present, although the most common reason for wanting to talk was to get their own questions answered. Prognosis was discussed less frequently with family members than were test results, treatment issues, and preventive strategies. Carer needs were almost never considered. Predictors of participation in the patient's medical encounters included older age and a greater physical impairment of patients, and increased involvement in diabetes-related and general care.

Among carers of community-living elderly patients attending hospital-based diabetes clinics in Birmingham [12], up to 90% reported providing help with instrumental activities of daily living, such as shopping, housework, preparing meals, finances and transport, and up to 25% help with personal care such as washing and bathing/showering, walking about outside, dressing/undressing, getting in and out of bed, and toileting.

As would be expected, when patients are less physically functional, when family members are spouses, when they provide more assistance with basic care, and when they have a greater understanding of diabetes management issues, family members are more likely to provide assistance with diabetes-related care [11]. Cognitive impairment is also a strong predictor of a greater need for the involvement of carers in supervising medication, monitoring blood glucose, and helping with personal care [37].

Using data from the Oldest Old Study, a nationally representative survey of people aged ≥70 years in the USA, Langa *et al.* [38] determined the weekly hours of informal caregiving received by community-dwelling elderly individuals with and without a diagnosis of diabetes. Those without diabetes received an average of 6.1 h of informal care, those with diabetes taking no medications received 10.5 h, those with diabetes taking oral medications received 10.1 h, and those on insulin received 14.4 h of care ($p<0.01$). Disabilities related to heart disease, stroke, and visual impairment were associated with a need for more diabetes-related care.

35.4 What effect can caring have on the carer?

The responsibilities of the caring role can take their toll on the physical, emotional, social, and economic well-being of the family and others closely involved in care provision [38–42]. Most published studies of the experience of significant others of people with diabetes have been about adults with type 1 diabetes. These show that relatives may be even more concerned and worried about the illness and its effects than the patients themselves [43, 44]. Carers often neglect their own health to provide care for family members. Spouses reported conflict about diabetes management and disturbed sleep [38]. Furthermore, the diabetes self-management behavior of husbands often deteriorated when conflict existed with their spouses [45].

Stodberg *et al.* [46] explored the "lived experience" of being a close relative (significant other) of persons with type 1 diabetes and identified four major themes:

I living in concern about the other's health
II striving to be involved
III experiencing confidence
IV managing (handling) the illness.

Many carers said that they lived a normal life and had come to accept diabetes as a normal part of life. At the same time, they felt they needed to be constantly attentive to how the person with diabetes was feeling, and lived their life waiting for the complications to come. They felt sorrow when they watched the health of the patient deteriorate and, whilst they had found ways to handle the illness, many felt they lacked adequate recognition and support from healthcare staff. When professionals took little notice of the significant others, carers felt humiliated, neglected, and uncertain as to how best they should care for the ill person. They had questions, but were not sure who to contact for advice.

The emotional burden of caring is a recurring topic in the caregiving literature [47]. Levels of low mood and anxiety, and rates of likely depression (21%) were as high, or even higher, in partners of European-American and Latino patients with type 2 diabetes as they were in the patients, especially if the partner was female [48].

Psychological distress in either partner either increases or is positively correlated with marital discord, hostility, and conflict which, in turn, decreases disease-related problem solving and marital satisfaction and can affect disease management and disease progression [49]. A study in Taiwan of the primary carers of elderly people with type 2 diabetes that used the SF-36 questionnaire to measure aspects of health-related quality of life found that the carers had a poorer mental but better physical wellbeing than the population norm [50].

A study of family caregivers of diabetes patients in Sudan, using the WHO 26-item quality of life measure, found that those who were younger, single, less-educated, and caring for people with more recently diagnosed illness were relatively vulnerable to the negative effects of caring [51]. This latter research group also published evidence that there was greater concordance between the impressions of family caregivers on the patient's quality of life in type 1 than type 2 diabetes, presumably because in those with type 1 diabetes it was easier to define the factors that adversely impacted on a patient's quality of life, such as diminished sexual desire or additional medical conditions [52].

People with diabetes complications are likely to require more care, which places an even greater burden on their carers. A small qualitative study found that the development of diabetic foot ulcers leads to both patients and carers experiencing a reduction in social activities, increased family tensions, lost time from work, and a negative effect on general health [53]. Another study of people with diabetic foot ulcers (mean age 60 years) and their carers from centers in the USA, UK, and Europe found that patient and carer scores on the SF-36 were closely correlated. Healing associated with a large improvement in the subscale related to emotional difficulties of the carers [54]. Starting insulin treatment for selected elderly people with type 2 diabetes with poor glycemic control on tablet therapy improved not only the patients' quality of life and mood, but also limited carer strain, as measured by the general health questionnaire [55].

Caring for a family member with a mental health problem has a significant impact on families [10]. Caring for a relative with dementia is associated with anger, grief, loneliness, and resentment, and can lead to elder abuse. People providing care for an older person who is depressed have poorer mental health and quality of life [56]. The frequency of behavioral disturbances predicts carer distress and plays a significant role in the carer's decision to put their relative into a care home. Thus it is important to regularly assess carers for psychological distress (see Table 35.2).

A UK study estimated the annual average financial cost to working-age carers of looking after someone with type 2 diabetes to be £1300, but when earnings were actually lost the cost was almost £11,000. Carers who lose earnings report higher levels of strain. Only one-third of carers reported receiving state benefits, and the shortfall between earnings lost and benefits received was substantial [57].

Not surprisingly, given that people who spend a lot of time together will share many lifestyle behaviors, non-genetically related partners of people with diabetes also have a greater than two-fold increased risk of being diagnosed with diabetes themselves during their lifetime compared to controls, and one in five display evidence of glucose intolerance [58].

While there is increasing support for a link between caregiver burden and diabetes, this requires further testing. For example, in a longitudinal study of frail elderly subjects in Japan, which included use of the Japanese version of the Zarit Caregiver Burden Interview, diabetes did not appear to feature as an independent predictor of caregiver burden [59].

35.5 What do carers want?

Families and friends involved in caregiving are often not prepared for the role and tasks they will need to undertake [6]. Carers describe their need for recognition, information, and advice to help them in their caring role, and adequate support services and respite when needed (Table 35.3). While many carers are eligible to receive formal care services, practical help from the family is often the preferred option. This is not due to dissatisfaction with formal services, but rather there is a general sense that while informal networks exist an atmosphere of normality can prevail [60].

Hennessy *et al.* [21] studied family members caring for elderly American Indians with diabetes to investigate diabetes care management, the challenges faced and the support services needed. The focus group participants reported a number of concerns, including anxiety about home care management, coping with psychosocial issues such as depression or non-compliance, decision

Table 35.2 Risk factors for carer psychological distress adapted from Shah *et al.* [10] and Carey *et al.* [74].

Caregiver factors	Risks
Age	Functional and cognitive changes associated with young or older age Caregiver burden, which may differ among ethnic groups Effects on health status that increase the risk of premature death, especially if the person they are caring for dies Physical and verbal abuse from relatives with cognitive behavioral problems
Gender	Women carers are more likely to become depressed than men Men may under-report their stress and caregiver burden
Health status	Physical health problems often predict caregiver depression Carers are also more likely to develop hypertension, cardiovascular events, and develop serious illness and all-cause mortality than people who do not provided care for family members
Ethnicity	Cultural beliefs and values have a significant impact on the caregiving experience, stress, psychological outcomes, and service use Caucasian caregivers report more depression than African Americans and Hispanic report more depression and behavioral problems then Caucasians and African Americans Some Asian cultures expect children to care for their older relatives (filial piety) but some of these factors are changing with an increasingly mobile population and other social reasons
Social support	If there is good social support and access to advice caregivers report less psychological distress and caring burden

The table focus on negative aspects of caring; however caregivers also report benefits such as spiritual and personal growth and shared time with the care recipient [75].

Table 35.3 What do carers want?

Respect and recognition as a partner in care
Timely explanation and relevant information
The right skills and expertise to manage and care
Knowing the options and what help is available
Practical support, especially the opportunity to take a break
Appropriate and flexible services, available when they are wanted
Adequate income

making, and communication with other family members. The findings would seem relevant to most informal carers trying to help and support older people with diabetes in the community.

A need for more information is the most common request of carers [61]. Subject to the consent of the older person, carers want timely education and advice about the specific health problems of the person they are caring for, what they can do to help, and the services available. Good information enables carers to become partners in the provision of care, and supports them in best helping the person they are caring for. Conversely, without information, carers are more likely to suffer from stress and consequently be less able to continue to care.

In Hennessey's study there was a perceived lack of information about the nature and expected course of diabetes, especially for those with co-morbid conditions, trepidation in handling tasks such as postoperative amputation care or coping with dialysis machines, and fears concerning the occurrence of a diabetic crisis. All of the carers emphasized the importance of developing and implementing efficient caregiving routines and mastering care techniques for successful diabetes care management. They looked for expert guidance and support on how this might be best achieved, and the implementation of diabetes education programs targeted at family caregivers was strongly recommended.

Although any information provided must include medical management of the disease, it is equally important that consideration be given to the social and practical management of diabetes within a family context.

Thus, diabetes education programs should also offer content on predictable psychosocial and behavioral problems encountered in diabetes care management with older adults, how these problems can be addressed within the family, and where help is available when family efforts have not been successful. Despite the increasing reliance on the internet for information provision, there still is little material on diabetes that is specifically targeted at carers. The family carers who participated in Hennessy *et al.*'s study highlighted some gaps they felt occurred in the provision and continuity of formal care services. The carers stated that they often felt stranded without sufficient professional back-up to enable them to provide care.

One common complaint was a difficulty knowing who to contact and obtaining a prompt response. Whilst the appointment of a case manager should address these issues, role or boundary restrictions are often cited as a reason for being unable to help. Sometimes carers are told that the case has been closed and they must go back to the end of the queue. The lack of an adequate response from professionals is short-sighted, as problems may then escalate and lead to carer breakdown and avoidable hospital admission, or a need for permanent nursing home care. Levine [62] described her sense of isolation and frustration with formal care providers in a personal account, entitled *The Loneliness of the Long-Term Caregiver*, where she said that it often felt as if "…she was challenging Goliath with a tiny pebble. More often than not, Goliath just puts me on hold."

Everyday problems such as substandard housing, a lack of modern conveniences, lack of financial resources, and reliance on others for transportation will exacerbate the burden on carers, as well as interfering with the ability to develop a routine for the cared-for person. A perceived absence of professional guidance or support in dealing with psychosocial problems will means that carers have to devise their own strategies for dealing with behavioral or psychological aspects of care, such as attempting to coax, cajole, or coerce patients into compliance with care regimens [21].

The importance of coordinating the activities of all family carers who provide assistance with diabetes care is also emphasized, with primary carers expressing frustration when they are unable to inform and synchronize the caregiving efforts of those involved. Periodically holding a family meeting with or without the participation of healthcare providers can be as an effective intervention to resolve or significantly improve the understanding of diabetes care requirements [21].

35.6 What are the benefits for carers?

People with chronic diseases are more likely to adhere to medical treatment if they have supportive family relationships [63], and this can improve outcomes [64]. Certainly, patients who feel supported and cared for report a greater sense of wellbeing [65], fewer depressive symptoms [66], and better general health [67]. However, family members seem to view diabetes as a more serious illness than those with the condition [68], and this lack of concordance can lead to conflict. It is important that any carer input does not undermine patient autonomy [14, 69].

There is some (albeit limited) research evidence that the involvement of family and friends in diabetes care can improve metabolic control and the management of complications. A systematic review of prospective intervention trials of social support on health outcomes in primary and outpatient care for type 2 diabetes identified six trials of adequate quality for review [70]. Most carried evidence in support of the idea that social support is influential on self-care and outcomes.

However, only three of the studies involved spouses, family or friends, and the mean age of the patients involved was only 59.3 years. During a 6-week educational program with older patients with diabetes, those with participating spouses, compared to those without, showed a greater improvement in diabetes knowledge and metabolic control [71]. In contrast, the participation of family and friends in diabetes education group sessions for Native Americans had no effect on metabolic control in women with type 2 diabetes [72]. Indeed, social support may have different effects for men and women. In the study conducted by Wing *et al.* [73], support from the spouse (in the same educational program) acted positively on weight loss for obese women with type 2 diabetes, while participating without the spouse worked out better for men.

In the observational study by Silliman [11], patients receiving more assistance from family members were more likely to report that they were taking their

Table 35.4 Potential benefits of networking and supported informal care.

Provision of additional social and emotional support
Increased availability and access to relevant healthcare information
Sharing of good clinical practice
Promotion of improved healthcare behaviors among both patients and carers
Increased mobilization of community-based diabetes resources
Provision of better opportunities for integrated diabetes education
Promotion of leadership qualities
Improved blood glucose management

medications as prescribed, that they were following their diabetes diets, and that there was some correlation between family member assistance and random glucose levels. There may be potential benefits of closer networking and greater support for carers, and these are listed in Table 35.4.

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CHAPTER 36
Public health issues and community impact

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KEY MESSAGES

- An aging population affects a society's health because of increased numbers of people and more years lived with disability.
- Diabetes exacerbates this burden because it is the seventh highest cause of years of life lost, and the 14th highest worldwide cause of disability-adjusted life years.
- Any restriction of activities of daily living creates a three-fold increase in costs compared with costs for those who are independent, and admission to a care home creates a nine-fold increase in costs.
- Diabetes has a profound societal effect on aging communities because of its functional impact.
- Clinicians must learn to recognize diabetes as a frailty-related entity, a transitional status preceding disability so that future intervention strategies will eventually lead to better functional outcomes.

36.1 Introduction

The ideal public health approach to diabetes would emphasize prevention and education for the whole community by:

- advocating for environments and policies that support healthy lifestyles, including healthy eating and physical activity
- preparing knowledgeable healthcare providers
- promoting access to resources for people with diabetes
- monitoring the effect of diabetes through data collection systems with emphasis on functional impact and recognizing frailty as a key issue.

36.2 Diabetes as a public health priority

36.2.1 Increasing prevalence of diabetes worldwide

The number of people with diagnosed diabetes in the world is rapidly increasing. The estimated global prevalence of diabetes in 2013 is 382 million. It is expected to affect 592 million people by 2035 [1].

36.2.2 Increasing diabetes prevalence with increasing age

Populations throughout the world show an increased prevalence of diagnosed and undiagnosed type 2 diabetes with increasing age, reaching a plateau in the very old. Data from Australia show that in the age group 25–34 years, 0.2% are diagnosed and 0.1% are estimated to have undiagnosed diabetes, in the age group 65–74 years the figures are 9.4% and 8.5%, and for people aged 75 and above they are 10.9% and 12.1% [2].

Data from the USA give prevalence rates of 20% in the 70–74 age range, 21% in the 75–79 age range, 20% in the 80–84 age range, and 17% in the 85 and above age range [3].

Data from nine European countries reported in the DECODE study report a prevalence of diabetes below 10% in people below 60 years of age and rates of 10–20% in the age range 60–79 years [4]. In Mexico in adults aged 60 and above the prevalence of diabetes is

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almost 25% compared with a prevalence of less than 1% in very young adults.

36.2.3 High prevalence of diabetes in care home residents

In the UK diabetes prevalence rates in care home residents are reported to be at least 16% and when testing is done for diabetes, rates of known and screen-detected diabetes rise to over 25%, with a further 25% showing impaired glucose tolerance [5]. Residents of care homes with diabetes have high levels of co-morbidity, disability, and frailty, and are at risk of significant polypharmacy [6].

36.2.4 Economic burden of diabetes in older people

The financial costs to the National Health Service (NHS) in the UK of diabetes have been estimated at £9.8 billion in 2010/11. Around 80% of this is spent managing complications. Based on the projected changes in the age structure and obesity levels of the population this will rise to £16.9 billion in 2035/6, assuming there is no inflation [7]. People with diabetes have medical costs that are two or three times that of age- and sex-matched people without diabetes, and this is thought to equate to an estimated extra spend of around £680 million in the UK, largely based on more hospital admissions, longer hospital stay once admitted, and more overnight admissions for planned procedures rather than day cases [8].

36.3 Heterogeneity of diabetes in the old

Age distribution at diagnosis has important repercussions on the health system and turns elderly diabetics into a heterogeneous population. Early cases of type 2 diabetes (before age 40) have increased the most. On reaching advanced age they will have been exposed to diabetes for several decades and many will have chronic complications. Hence many will become dependent and their treatment will be complex. On the other hand, cases arising after age 70 have a lower rate of microvascular complications, and their glucose is easily controlled, mostly with low doses of oral hypoglycemic agents. The profile of the elderly diabetic patient is thus heterogeneous and can range from being asymptomatic (with a low risk of late complications) to disabling disease [9]. A very old patient cannot be treated strictly in accordance with the general diabetes guidelines. Rather, interactions between the diabetes and such geriatric syndromes as, for example, dementia, depression, incontinence, and immobility also need to be taken into account. In the first instance our concern is to improve the patient's wellbeing and his/her quality of life. It is necessary to tailor not only pharmacotherapy, but also general therapeutic measures to the specific situation of the individual patient. In early-onset diabetics, aging interacts with hyperglycemia to accelerate the onset of late complications, such as retinopathy and nephropathy, with their onset occurring within 5 years of the diagnosis of diabetes. Older people with diabetes, over the age of 70 years or living in care homes, are more likely to develop hyperosmolar non-ketotic coma. Nevertheless, diabetes continues to shorten life, even in older people [10]. Diabetes is associated with a greater disease burden at all ages, even in people in care homes who have diabetes. People with diabetes also report poorer functional status than those who do not have diabetes.

36.4 Epidemiology

An aging population affects a society's health because of increased numbers of people and more years lived with disability. Diabetes exacerbates this burden: it is ranked as the seventh highest cause of years of life lost and the eighth highest cause of disability-adjusted life years in western countries, and the 14th highest worldwide cause of disability-adjusted life years [11]. Any restriction of activities of daily living creates a three-fold increase in costs compared with costs of those who are independent, and admission to a care home creates a nine-fold increase in costs [12].

The countries with the largest number of people with diabetes are China, India, USA, Brazil, and Mexico. The regions with the highest prevalence of diabetes are the Pacific Islands and the Middle East. As type 2 diabetes is predominantly more prevalent in aging populations, this creates a major public health burden. In Mexico diabetes afflicts an estimated 9% of the population, a rate that has increased by 15% from 2006 to 2012. In the UK diabetes currently affects 6% of population, a rate that has doubled over the past 10 years [13]. Diabetes mellitus accounted for 22.6 million disability adjusted life years (DALYs) in older people in 2010,

80% of the burden arising in low-income and middle-income regions. The burden in older people is forecast to increase by 96% from 2004 to 2030 [14]. In NHANES 1999–2002 [15], the prevalence of total (diagnosed and undiagnosed) diabetes increased sharply with age, from 2.5% in people aged 20–39 years to 21.6% in people aged 65 years and older. The prevalence of total diabetes rose from 5.1% (1988–1994) to 6.5% (1999–2002), with the largest increases occurring in the oldest age groups. Few epidemiological studies of diabetes in older people have been done in low-income and middle-income countries. Nationally representative surveys in China in 2007–2008 [16] and Mexico (Encuesta Nacional de Salud y Nutrición 2012) [17] provide age-stratified estimates for older adults. In China, total diabetes prevalence rose from 3.2% (20–39 years of age) to 20.4% for people aged 60 or older. Prevalence was lowest in the least economically developed rural settings. In Mexico, total diabetes prevalence was 0-82% at 20–29 years of age rising to 25% at ages 60–79 years. From this prevalence, more than 40% of the people with diabetes in Mexico were estimated to be aged 60 and older. The detection and control of diabetes in older people is suboptimum. In the USA NHANES surveys, of the proportion of cases that were diagnosed, 70% was similar across all age groups [18]. In the China national survey, no age-stratified data were provided, but in the sample as a whole only 31% of cases were diagnosed. In a Mexican national survey, the proportion of people diagnosed rose with age, from roughly two-thirds of people under 50 years, reaching 86% of people aged 60–69 years, 87% of people aged 70–79 years, and 80% of people aged 80 years or older. However, the proportion of diagnosed cases controlled was lower in older than in younger participants: 58% in those aged 60–69 years, 45% in those aged 70–79 years, and 50% in those aged 80 years or older.

The economic burden of diabetes is quite significant: Canada spends $9 billion annually on health care, disability, work loss, and premature death costs related to diabetes. An American study suggested that 14% of the US healthcare budget (or one in seven US health-care dollars) is spent on diabetes. With the anticipated increase in people developing diabetes, the world is expected to have an increasingly heavy economic burden related to the treatment of diabetes and its complications. A person with diabetes typically has medical costs that are two to five times higher than costs for a person without diabetes. Treating and managing diabetes can amount to $4500 per year for each person with the disease. People with diabetes are at high risk of developing complications. Treating these complications is more expensive to the health system than intensively managing the disease and preventing complications. For example, cost-effectiveness studies on preventing diabetes show a reduction of $877,000 in annual treatment costs for every 1% increase in the number of Canadians who are physically active [19]. The person with diabetes has numerous medical and personal costs related to the care and management of the disease. Improving and maintaining glucose levels is critical to prevent or delay long-term complications. Medical costs associated with controlling glucose levels such as medications, surveillance, as well as dietary changes, can be prohibitive without insurance or government coverage. Other costs for medical treatment can include transportation to health facilities, lodging, and child care. Indirect costs include decreases in productivity due to absence from work, decreased earning potential because of potential complications and disabilities, lost earnings due to premature death or retirement, and increased insurance costs.

36.4.1 Risk factors

The causes of diabetes are not fully understood. It is believed that environmental factors and behavioral patterns often hasten the disease in genetically susceptible people. The interaction between genetic and environmental risks varies among populations and ethnic groups. By changing environmental risk factors, people can reduce their risk of developing type 2 diabetes. By increasing awareness of diabetes and identifying people at risk of the disease, high-risk behaviors can be modified to prevent or delay type 2 diabetes.

36.4.2 Socioeconomic issues

Studies show an association between diabetes and socioeconomic status. Developed countries report more diabetes among people with low incomes and low education. These people may be limited in their ability to select healthier diets and may be less aware of the benefits of physical activity. Many people living on a low income have limited food choices, relying on food-banks or whatever is available on the street. Physical activity is less of a priority than worrying about the next meal or a place to sleep. In middle-income countries like

Mexico, the lowest prevalence is found in the lower income population and people in the highest income level have prevalence above the mean for the general population. This can be partly attributed to lower awareness of the condition but in rural areas with very low income the prevalence is clearly lower [20].

36.4.3 Conceptual framework of risk factors for the development of diabetes

36.4.3.1 Demographic characteristics

Diabetes can appear at all ages and in all ethnic groups and has been found in virtually all parts of the world. Indeed, from a global perspective, diabetes has become an epidemic.

36.4.3.2 Social group effects

Diabetes is strongly associated with socioeconomic transition; the prevalence of diabetes in the developed countries (6.2%) is almost double that in the developing countries (3.5%). Furthermore, the increase in prevalence of diabetes over the next 25 years will be much greater in the developed countries, which will experience a 170% increase compared with a 42% increase in the developing countries. The USA has the largest number of diabetics of all the developed countries, with more than 16 million currently suffering from the disease [21]. Over the past 40 years, the prevalence of both diagnosed and undiagnosed diabetes has increased dramatically, as has the prevalence of impaired fasting glucose and impaired glucose tolerance, both precursors of diabetes. Although diabetes can affect any segment of the population, the disease is especially burdensome among certain groups, particularly those of Black African origin, Latin Americans, Native Americans, the elderly, those in lower socioeconomic classes, and women. These groups are also least likely to receive timely and adequate health care; among them, as a result, diabetes is somewhat of a hidden disease. For women in particular, diabetes can have devastating effects on health. Diabetes effectively eliminates the protection that women generally experience against coronary heart disease because hyperglycemia and hyper-insulinemia undermine the protective effects of estrogen.

36.4.3.3 Genetic risk factors

Heredity plays a significant role in the development of type 2 diabetes. Certain ethnic groups, such as Aboriginal, African, Latin-American, and Asian, have a rate of type 2 diabetes that is two to six times greater than that found in the Caucasian population. The rates of kidney failure, amputations, and eye disease are also significantly higher for these groups. The risk factors of family history, insulin resistance, obesity, history of diabetes related to pregnancy, impaired glucose tolerance, and physical inactivity are equally distributed between all populations. The disproportionate impact of diabetes among different ethnic groups may be the result of genetic risk factors interacting with environmental risk factors.

36.4.3.4 Lifestyle

The risk of developing type 2 diabetes also increases with body weight and sedentary lifestyle.

36.4.3.5 Obesity

Being overweight is the most recognized environmental trigger for type 2 diabetes. Obesity is found among 80% of people with this disease. Some studies have also identified an association between certain genes linked to obesity and type 2 diabetes. Diabetes is associated with the level and duration of obesity, as well as type of body fat distribution. A body mass index (BMI) greater than 27 signifies risk for the development of diabetes.

36.4.3.6 Age

The incidence of type 2 diabetes increases with age. Half of all new cases of type 2 diabetes occur over the age of 55. As people age, insulin resistance increases. Older people tend to have physical limitations on their ability to exercise and tend to gain weight as they age, further increasing their risk for diabetes.

36.4.3.7 Physical activity

Type 2 diabetes is often found among people who lead inactive, sedentary lifestyles. Research has shown that non-obese people living in cities are more likely to develop type 2 diabetes than non-obese people living in rural areas. This relates to the difference in physical activity between city and country dwellers.

36.4.3.8 Diet

Excess food energy intake is associated with obesity, a risk factor for type 2 diabetes. Decreased sensitivity to insulin and glucose intolerance are linked to a diet low in fiber and high in saturated fat.

36.4.3.9 Cholesterol abnormalities and high blood pressure

The development of type 2 diabetes is associated with high levels of LDL cholesterol, low levels of HDL cholesterol, and pre-existing blood vessel disease. In addition, people with high blood pressure appear to have an increased incidence of type 2 diabetes. More frequent and/or earlier screening for diabetes is recommended for people with cholesterol abnormalities and/or high blood pressure.

36.4.3.10 Psychological factors

Distress and psychological distress also have negative influences on glycemic control once diabetes has developed. Old diabetics are more likely than non-diabetics to experience clinical depression [22], and even when clinical depression is not present, diabetic adults are more than twice as likely to manifest substantially higher rates of depressive symptoms and other signs of psychological distress. Depressed diabetics are more likely to develop diabetic complications, co-morbid chronic health conditions, and disability than non-depressed diabetics, and are as much as four times more likely to die prematurely. The presence of depression was strongly associated with hospitalization and mortality. Depression needs to be treated aggressively in older people with diabetes to improve compliance [23].

36.4.3.11 Other clinical aspects

Clinical aspects complicating diabetes care in older people include cognitive decline, physical functional decline, and frailty.

Functional status. Older diabetic patients report reduced physical function compared with other older people as a result of multifactorial impairment, which includes visual deterioration, peripheral neuropathy, and balance problems. In the oldest old, community-dwelling individuals without evidence of severe functional impairment at baseline, diabetes increases the risk of incident disability in only 2 years [24].

Frailty is considered a syndrome of decreased reserve and resistance to stressors and is clinically expressed as muscle weakness, poor exercise tolerance, sarcopenia and disability. There is a close relationship between age-related metabolic changes and the occurrence of co-morbidities that may lead to frailty. The downward spiral of frailty is accelerated in older people with type 2 diabetes, and it is reversible with appropriate interventions. Frailty encompasses diverse complications already associated with diabetes. Frailty is associated with cognitive impairment, reduced ability to perform activities of daily living, and increased expression of inflammatory and coagulation markers that may contribute to the adverse microvascular effects of diabetes. Although glycemic control remains the main target in type 2 diabetes in robust older persons, this is not appropriate for those with frailty. Frail elderly people with type 2 diabetes are a specific group in need of treatment parameters for both initial and maintenance therapy with oral antidiabetic agents.

Cognitive impairment. In a recent meta-analysis of 25 prospective studies [25], patients with diabetes had a 1.5-fold greater risk of mild cognitive impairment (MCI) and a 1.6-fold greater risk of dementia compared to people without diabetes. Glycemic control and duration of diabetes are important factors related to the development of cognitive impairment in patients with type 2 diabetes. According to a study in menopausal females with diabetes, an increase in the level of HbA1c by 1% is associated with a 1.5-fold greater risk of developing MCI, and a 1.4-fold higher risk of developing dementia [26]. Some possible mechanisms for hyperglycemia-induced cognitive impairment include cerebral macro- and microvascular alterations due to hyperglycemia.

Loneliness and social isolation. Loneliness has been reported by as many as 47% of European diabetic elderly. In patients without ADL impairments, 60% were in need of assistance, compared to 95% among those with more than one impairment ($p<0.01$). Among them, cognitive impairment tends to be more common (19%), as well as other conditions such as chronic pain (63%) [27].

36.5 Prevention

36.5.1 Evidence for the prevention of type 2 diabetes in older people

There is good evidence from good-quality randomized controlled trials that in people with impaired glucose tolerance (IGT) who are at high risk of developing diabetes, progression to diabetes can be prevented or delayed. In the USA Diabetes Prevention Program (DPP) over 3000 adults with IGT were randomized to an intensive lifestyle intervention targeting weight reduction and increased physical activity, or metformin

therapy or normal management (control group) Those in the lifestyle group achieved a 58% reduction in progression to diabetes compared with controls, and those on metformin achieved a 31% reduction compared with controls [28]. The effect of lifestyle modification was greatest in people aged 60 or above, whereas the effect of metformin in this group was not significant. The DPP cohort was followed for a further 10 years and this confirmed that the group aged 60 and above appeared to benefit more from the lifestyle intervention than did younger participants and that this age group did not appear to benefit from metformin [29].

It must be noted that prevention studies enroll relatively healthy older adults and do not enroll many people aged over 70 years, nor those with functional or cognitive impairment.

We may conclude that there is good evidence for lifestyle change as an intervention to prevent diabetes in older people at high risk, but that there is little evidence for prescribing metformin and none in older people with functional or cognitive impairment.

The following preventive levels should be considered:

- *Primary prevention*. Lifestyle holds the potential for reducing the risk of elders developing type 2 diabetes. Older adults' lifestyle choices dramatically influence their risk for developing type 2 diabetes. With such compelling information, promoting preventive lifestyle strategies should be part of routine healthcare for older adults, including weight loss, healthful eating, and physical activity.
- *Secondary prevention*. Complications of diabetes are not inevitable; they can be reduced with careful management. Awareness is the first step; currently 35–44% of people with diabetes don't know they have it.
- *Tertiary prevention*. Efforts must be addressed at limiting functional impact.

Recommendations have been proposed for prevention in high-risk individuals. The International Diabetes Federation global guideline for older people with type 2 diabetes outlines these processes for diabetes prevention (see Box 36.1).

Box 36.1 IDF Categories for Recommendations

Category 1: Functionally independent. Consider offering a lifestyle change intervention program to older people who are at high risk of developing diabetes, especially those with impaired glucose tolerance, elevated fasting glucose, or HbA1c between 6.1% and 6.4% (43–46 mmol/l).

Category 2: Functionally dependent. If frail, a tailored home-based lifestyle/exercise program may assist to reduce the risk of diabetes in high-risk individuals. Lifestyle changes should not include dietary changes which may result in weight loss. If demented, any lifestyle changes should be tailored to allow for the high risk of lack of cooperation by the individual with dementia and the need for family and/or caregiver support.

Category 3: End-of-life care. Interventions to prevent diabetes are unlikely to be relevant for those at the end of life.

36.5.2 Challenges to preventing diabetes and its complications

Seniors are especially at high risk for developing diabetes. As they age, seniors are less likely to be physically active, either by choice or because of disabling conditions. The risks of obesity and abdominal fat accumulation are increased. The combination of high-risk factors and the aging process increases the occurrence of type 2 diabetes with age. The rate of diabetes is increasing along with the growth of the aging population. Type 2 diabetes is a major cause of disability and death in the elderly. The disease is often difficult to diagnose in the elderly population. Symptoms of hyperglycemia may not appear at first and the symptoms are generally non-specific, such as fatigue, depression, and failure to thrive. Because of this, seniors often have already developed long-term complications before being diagnosed. Diabetes can be particularly life-threatening in the frail elderly. Seniors with diabetes who are generally healthy should aim for blood glucose levels that will reduce the development and progression of complications. Seniors with other health problems should avoid both high and low blood sugar levels because either extreme can complicate their fragile health.

There are a variety of challenges to consider when addressing the needs of seniors with diabetes. Some seniors on fixed incomes may be unable to afford the medication, food, and support services needed for managing diabetes.

Access to services and appointments because of physical limitations or minimal transportation services could be limited. Older people can often become depressed from isolation, which can lead to obesity, malnutrition, and minimal physical activity. The lack of coordination in services can be confusing for seniors

who need support from community and health professionals. Seniors with diabetes may need someone who can voice their needs if their condition deteriorates and they are unable to care for themselves.

36.6 Putting it into practice: An agenda for action

As far as we are aware there are no programs to prevent diabetes specifically in older people in any countries in the world. A number of countries have developed or are developing policies to prevent diabetes in all age groups.

In the UK the National Institute for Health and Clinical Excellence (NICE) has reviewed all the published evidence and in 2011/12 produced two sets of guidelines: *Preventing type 2 diabetes: population and community interventions* (NICE PH 35) and *Preventing type 2 diabetes: risk identification and interventions for those at high risk* (NICE PH 38) These two guidelines do not specifically deal with older people, but the principles are likely to apply to fit healthy older people. For individuals PH 38 lists the following recommendations [30]:

1. Risk assessment: setting up systems.
2. Encouraging people to have a risk assessment.
3. Risk identification: using a validated computer-based risk assessment tool which provides a validated risk-assessment questionnaire. This recommendation specifically says that people aged 75 and over should not be excluded.
4. Risk identification: using a venous blood test (fasting glucose or HbA1c) for adults with high risk scores obtained from the risk assessment tool.
5. Matching interventions to risk.
   - a. For those at low risk offer brief advice to improve lifestyle.
   - b. For those at moderate risk (a high risk score but fasting glucose less than 5.5 mmol/l or HbA1c less than 6% (42 mmol/l) tell the person they are at moderate risk, offer a brief intervention to help them change their lifestyle, for example a walking program or slimming club, and discuss whether they want to join a structured weight-loss program and if they want this signpost them to it.
   - c. For those at high risk (a high risk score and fasting glucose of 5.5–6.9 mmol/l or HbA1c of 6–6.4% (42–47 mmol/l)). Tell the person they are at high risk but that does not mean they will necessarily mean they will get type 2 diabetes. Offer them referral to a local, evidence-based, quality-assured intensive lifestyle change program.
6. Reassessing risk: develop a call and recall system to review using the two-stage risk assessment.
   - a. For those at low risk: every 5 years.
   - b. For those at moderate risk: every 3 years.
   - c. For those at high risk: every year.
7. Commission risk identification and intensive lifestyle change programs.
8. Quality-assured, intensive lifestyle change programs: design and delivery. They should be for 10–15 people per program, be delivered by practitioners with relevant knowledge and skills, have a person-centered empathy building approach, meet at least eight times over 9–18 months, and offer follow-up sessions, for example every 3 months, for at least 2 years after the initial program period.
9. Quality-assured, intensive lifestyle change programs: content. This should be designed to encourage people to undertake a minimum of 150 min of moderate intensity physical activity per week to gradually lose weight.
10. Quality-assured, intensive lifestyle change programs: evaluation.
    - a. Programs need to be evaluated at least every 12 months for a number of variables, including attendance, changes in weight and physical activity of participants, HbA1c change, and delivery of the program.
11. Raising awareness of the importance of physical activity. Explain that 150 min of moderate physical activity is recommended.
12. Provide tailored advice on physical activity.
13. Weight management advice.
14. Dietary advice.
15. Vulnerable groups: information and services. These include people with severe mental health problems, those with learning disabilities, and those with physical or sensory disabilities.
16. Vulnerable groups: supporting lifestyle change.
17. Intensive lifestyle-change programs: quality assurance. Set up a national accreditation body to benchmark, audit, accredit, and share effective practice in type 2 diabetes prevention.
18. Training and professional development. The national accreditation body should work with others to

Box 36.2 Key aspects of preventative programs

- Supporting behavior change
- Achieving and maintaining a healthy weight
- Effective weight-loss programs
- Increasing physical activity
- Cultural appropriateness

provide training to healthcare professionals to deliver all the recommendations.

19 Metformin. Use clinical judgment on whether (and when) to offer metformin to support lifestyle change for people whose blood tests are deteriorating if this has happened despite their participation in an intensive lifestyle change program or if they are unable to participate in such a program.

20 Orlistat. Use clinical judgment on whether to prescribe orlistat to people with a BMI of 28 or more as part of an overall plan for managing obesity.

There has been no extra money to support the implementation of these recommendations and they have as yet not been widely adopted in the UK. The general recommendations have been enacted in primary care, but there have been very few intensive lifestyle change programs set up, and there is no national accreditation body set up to develop this work.

PH 35 lists five guiding principles [31] (see Box 36.2) and recommendations as follows:

1 Integrate national strategy in non-communicable disease.

2 Local joint strategic needs assessments.

3 Develop a local strategy.

4 Interventions for communities at high risk of diabetes.

5 Convey messages to the whole population.

6 Convey messages to the local population.

7 Promote a healthier diet: national action. This involves working with partners, including the commercial sector, to promote the provision of healthier food choices. It includes working with manufacturers of prepared foods to reduce calories, decrease saturated fat, and decrease salt content. It also includes working with food manufacturers and retailers to provide clear, non-ambiguous, and consistent calorie information on food.

8 Promote a healthier diet: local action. This includes providing information on how to produce healthier meals and snacks on a budget. It also includes helping people to be aware of their eligibility to welfare benefits such as free school meals, free school fruit, and Healthy Start food vouchers.

9 Promote physical activity: national action. This includes using planning regulations to maximize opportunities for physical activity. It also includes using planning guidance to ensure physical activity is a primary objective of transport policy and the wider built environment.

10 Promote physical activity: local action. This includes providing open green space for physical activity.

11 Train those involved in promoting healthier lifestyles.

Cultural appropriatenessAgain there has been no new money to support the implementation of these recommendations in the UK and many of them therefore remain aspirational. There has been some controversy as to how much government can and should do to promote healthy eating through legislation, such as taxing sugary drinks and energy dense fast food, and how much can and should be done by voluntary agreement with the food industry. Similar debates have been occurring in a number of countries throughout the world.

36.7 Summary

In this chapter, we have reviewed evidence that diabetes has a profound societal effect on aging communities because of its functional impact. The personal health burden is also substantial. This evidence should prompt the development in clinicians of new skills in functional assessment and comprehensive management in order to achieve meaningful progress in the quality of care for older people with diabetes. This will be achieved through major changes in attitudes and clinical behavior by health and social care staff. Such a change must have a long-term impact. Clinicians must learn to recognize diabetes as a frailty-related entity, a transitional status preceding disability, so that future intervention strategies will eventually lead to better functional outcomes.

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CHAPTER 37
Providing cost-effective diabetes care

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KEY MESSAGES

- An aging population requires increased government spending on health care due, in large part, to an increased prevalence of non-communicable diseases (i.e., dementia, heart disease, and osteoarthritis) and disability associated with advanced age.
- Older adults with diabetes are at substantial risk for microvascular and cardiovascular complications of the disease, and the disease is linked to reduced functional status, increased risk of institutionalization, and higher mortality.
- In a US analysis, approximately 85% of direct medical costs by older adults were due to hospital inpatient stays, prescription medications (excluding diabetes medications), nursing/residential facility stays, and physician's office visits.
- The DPP Research Group reported that, from a payer perspective, lifestyle was cost-effective and metformin was marginally cost-saving compared with placebo over 10 years.
- Results suggest that intensive glucose control may not be cost-effective in patients who are very old.
- Our knowledge relating to diabetes care in older adults is still limited on several fronts: no large-scale interventions studying diabetes care in oldest adults (e.g., persons older than 75 years) are available, evidence of benefit and harm from intensive glycemic control is limited and inconsistent, evidence for lipid lowering is limited, evidence of an optimal diabetes care delivery model is lacking so that no recommendation is available, and little evidence is available to support metabolic or educational interventions for long-term care residents or those who are housebound.

37.1 Introduction

Population aging is occurring in both developed and developing countries due to declining mortality and fertility rates. The percentage of the global population composed of older adults (aged 60 or older) increased from 9.2% in 1990 to 11.7% in 2013, and will continue to grow, reaching 21.1% by 2050 [1]. In numeric terms, the global population of older adults is expected to more than double, from 841 million people in 2013 to more than 2 billion in 2050.

Population aging has major social and economic consequences. An aging population requires increased government spending on health care due, in large part, to an increased prevalence of non-communicable diseases (i.e., dementia, heart disease, and osteoarthritis) and disability associated with advanced age. These diseases and disabilities also create a burden for the families of older adults who provide informal caregiving outside of the healthcare system. Among all non-communicable diseases, diabetes is one of the most prevalent with over 25% of individuals age 65 or older living with the disease in the USA (11.8 million with diagnosed and undiagnosed diabetes) [2]. Older adults with diabetes are at substantial risk for microvascular and cardiovascular complications of the disease, and the disease is linked to reduced functional status, increased risk of institutionalization, and higher mortality [3]. The burden of diabetes raises important concerns regarding the costs of preventing and managing diabetes and its associated complications.

In light of the challenges that many countries face in controlling the costs of diabetes, we review what is known and not known about the cost-effectiveness

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of specific elements of diabetes prevention and management in older adults.

37.2 Current and future costs of diabetes

Diabetes accounts for an estimated 32% of all Medicare spending in the USA. The total national cost of diabetes in the USA was estimated at $245 billion in 2012 based on national public and private data sources [4]. This total cost consists of $176 billion in direct medical costs and $69 billion in reduced productivity. Government insurance, including Medicare, Medicaid, and the military, covered 62.4% of diabetes care costs in 2012. Of the $176 billion in direct medical costs, an estimated $104 billion was incurred by adults aged 65 years or older. Approximately 85% of these direct medical costs by older adults were due to hospital inpatient stays ($48 billion), prescription medications (excluding diabetes medications) ($19 billion), nursing/residential facility stays ($12 billion), and physician's office visits ($9 billion) [4].

Apart from the direct costs of diabetes in older adults, indirect costs for diabetes and diabetic complications among older adults are significant. A nationally representative survey of adults aged 70 years or older found that older adults with diabetes required an average of 10.5–14.4 h of informal caregiving per week, compared to only 6.1 h per week for those without diabetes ($p<0.01$) [5]. The costs of informal caregiving were estimated to be equivalent to $3–6 billion per year in the USA.

As a result of the aging of the US population and the increasing prevalence of obesity, healthcare costs associated with diabetes are expected to grow significantly. Earlier forecasting studies have projected that the number of older individuals with diagnosed diabetes will rise from 6.5 million in 2009 to 14.1 million in 2034 [6]. Medicare spending on diabetes care has been estimated to triple over the 25-year period, from $45 billion in 2009 to $171 billion in 2034.

37.3 Prevalence of pre-diabetes and diabetes prevention

In addition to the high rates of diabetes in the older adult population, half of this population meet criteria for pre-diabetes [7]. Because of the size of the older adult pre-diabetic population, the importance of preventing the progression of diabetes in the older adult population is significant.

The Diabetes Prevention Program (DPP) is the largest trial that has evaluated the role of lifestyle interventions and medications in preventing diabetes [8]. The overall study enrolled more than 3000 adults, about 20% of whom were aged 60 years or older. The mean age of older adults in the DPP was 66.4 years, ranging from 60 to 85 years. The study population had good representation among older adults in their mid-60s but far less participation from adults aged 70 years or older. This study found reductions in the incidence of diabetes with lifestyle intervention and metformin treatment after 2.8 years of follow-up. The relative risk reduction of incident diabetes with the lifestyle intervention was largest for adults aged 60 years or older compared to adults aged 25–44 years and 45–59 years (71% vs 48% and 59%, respectively). Interestingly, the oldest adults did not experience reductions in diabetes incidence with metformin, while younger subjects did [9]. Ten-year follow-up data from the DPP provided evidence for the persistent benefits of lifestyle intervention compared to drug therapy in older adults [10], as well as secondary benefits of lifestyle intervention, including reductions in urinary incontinence [11] and improvements in quality of life [12].

37.4 Principles of cost-effectiveness analysis

In the face of resource constraints, healthcare systems are seeking novel approaches to limit the growth of healthcare costs. Innovative interventions in diabetes prevention, diagnosis, and treatment may improve patients' outcomes and quality of life, but may come at additional costs. The economic impact of diabetes-related interventions has received increased attention in the medical literature. It has become critical to understand the potential costs and benefits of each intervention through economic evaluations to determine whether an intervention provides good value.

Cost-effectiveness analysis (CEA) provides a standard methodological tool for determining whether a medical service or intervention provides good value for money [13]. CEA is a comparison between two or more alternative methods of approaching a health problem.

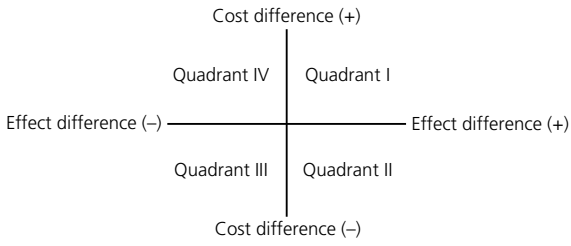

Figure 37.1 Cost-effectiveness plane.

The alternative to a new intervention can be the usual care that would be given if the new intervention were not used at all. Results of CEA are presented as incremental cost-effectiveness ratios (ICERs). The ratio is calculated as the difference in costs (net costs) between the alternatives divided by the difference in health outcomes (net effectiveness).

The ICER requires careful interpretation as the same ratio can have divergent conclusions. Figure 37.1 shows a cost-effectiveness plane, a graphical demonstration of cost-effectiveness comparisons. The *x*-axis represents the scale of effect differences, the *y*-axis represents the scale of cost differences, and the point where the *x*- and *y*-axes intersect is the starting point of both effectiveness and costs for the reference comparator. Each intervention alternative to the reference comparator is represented by a point placed on the plane to indicate how much more or less it costs than the comparator does (reading from the *y*-axis), and how much more or less effective it is than the comparator is (reading from the *x*-axis). For example, if a new treatment is more effective and less costly than usual care, the point representing the new treatment will fall into quadrant II. Any alternatives appearing in quadrant II are considered cost saving. If an alternative falls into quadrant I, it means that the alternative is more effective but a higher cost than usual care. Policy makers will have to decide if the gain in effectiveness is worth the additional costs in this case.

The measure of health outcomes can take different forms, such as years of life gained or specific clinical events such as cases of HIV. To standardize CEA across conditions and interventions, public health bodies have advocated the use of quality-adjusted life years (QALYs) [14] as a health outcome that integrates both length and quality of life. Cost-utility analysis (CUA) is a type of CEA in which health outcomes are measured in terms of QALYs [15].

It is crucial to determine an appropriate perspective before a CEA is conducted. The choice of the perspective affects what health outcomes and resources are relevant and how they should be measured and valued in the CEA. The CEA usually assumes the societal perspective with the idea of maximizing net health benefit for all members of a population within limited resources. When a CEA is conducted from the societal perspective, it should consider everyone affected by the intervention and count all significant health outcomes and costs that flow from it, regardless of who experiences the outcomes or costs. The measure of health outcomes needs to be wide-ranging and to include longer life, better function, and unwanted side effects. Costs should include not only medical and other resources, but also the time of patients and unpaid caregivers.

If a CEA is conducted from other perspectives, some outcomes and costs can be reasonably omitted if they are not of interest to the policy maker. For example, a CEA conducted for a health educational program might consider only the health outcomes experienced by the program's beneficiaries and the costs paid by the program, and not outcomes or costs experienced by others [13].

37.5 Cost-effectiveness of diabetes prevention

The DPP Research Group conducted a within-trial CEA of lifestyle intervention or metformin for the primary prevention of type 2 diabetes [16]. The research group summarized direct medical costs, direct non-medical costs, and indirect costs associated with the DPP interventions (lifestyle, metformin, and placebo) over 3 years, and calculated the costs of the lifestyle and metformin interventions relative to the placebo intervention and the costs of the lifestyle intervention relative to the metformin intervention from the perspectives of a large health system (payer) and society [17].

The investigators found that the lifestyle intervention cost $15,700 per case of diabetes delayed or prevented and $31,500/QALY gained from a health system perspective, and cost $24,400 per case of diabetes delayed or prevented and $51,600/QALY gained from a societal perspective (all costs were expressed in year 2000 US dollars). The metformin intervention cost $31,300 per case of diabetes delayed or prevented and $99,600/

QALY gained from a health system perspective, and cost $34,500 per case of diabetes delayed or prevented and $99,200/QALY gained from a societal perspective. The DPP Research Group concluded that over 3 years, both of the lifestyle and metformin interventions were effective as well as cost-effective from the perspective of a health system and society. Both interventions are likely to be affordable in routine clinical practice, especially if implemented in a group format and with generic medication pricing. Their findings also suggested that lifestyle intervention was more cost-effective than the metformin intervention. In other words, the metformin intervention was "dominated" by the lifestyle intervention in economic terms and should not be adopted if only cost-effectiveness is considered. However, the metformin intervention may still be a worthwhile option for delaying or preventing type 2 diabetes when treatment availability, health insurance coverage, and patient and provider preferences are considered [16].

When stratified by age, the lifestyle intervention per case of diabetes prevented during the trial cost $4300 less for persons aged 60 years or older than for those aged 45 years or younger from a health system perspective, and it cost $6700 less from a societal perspective. The metformin intervention per case of diabetes prevented during the trial cost $224,000 more for persons aged 60 years or older than for those aged 45 years or younger from a health system perspective, and it cost $247,000 more from a societal perspective.

In a subsequent study with longer follow-up time, the DPP Research Group reported that, from a payer perspective, lifestyle was cost-effective and metformin was marginally cost-saving compared with placebo over 10 years [18]. The cumulative, undiscounted per capita direct medical costs of the interventions, as implemented during the DPP, were $4601 for lifestyle, $2300 for metformin, and $769 for placebo. The cumulative direct medical costs of care outside the DPP were least for lifestyle ($24,563 for lifestyle, $25,616 for metformin, $27,468 for placebo). The cumulative, combined total direct medical costs were greatest for lifestyle and least for metformin ($29,164 lifestyle, $27,915 metformin, $28,236 placebo). The cumulative QALYs accrued over 10 years were 6.81 for lifestyle, 6.69 for metformin, and 6.67 for placebo. When costs and outcomes were discounted at 3%, lifestyle cost $10,037/QALY, and metformin had slightly lower costs and nearly the same QALYs as placebo. No age-stratified results were reported.

Using Markov simulation models to estimate progression of disease, costs, and quality of life, Herman *et al.* estimated the lifetime cost-utility of the DPP interventions for the DPP cohort 25 years of age or older with impaired glucose tolerance [19]. Compared with the placebo intervention, the lifestyle and metformin interventions were estimated to delay the development of type 2 diabetes by 11 and 3 years, respectively, and to reduce the absolute incidence of diabetes by 20% and 8%, respectively. The cumulative incidence of microvascular, neuropathic, and cardiovascular complications was reduced and survival was improved by 0.5 and 0.2 years. Compared with the placebo intervention, the cost per QALY was approximately $1100 for the lifestyle intervention and $31,300 for the metformin intervention. From a societal perspective, the interventions cost approximately $8800 and $29,900/QALY, respectively. From both perspectives, the study concluded that lifestyle intervention dominated the metformin intervention. The results of sensitivity analysis show that the lifestyle intervention was cost-effective in all age groups, but the metformin intervention did not represent good use of resources for people older than 65 years of age.

37.6 Cost-effectiveness of specific components of diabetes care

Evaluating whether interventions are cost-effective and yield acceptable benefits is important. Various types of treatment interventions in diabetes care have been evaluated.

37.6.1 Glucose control

Blood glucose control reduces the risk of developing the eye, nerve, and kidney complications of diabetes. The CDC Diabetes Cost-effectiveness Group used a Markov model of type 2 diabetes disease progression to estimate incremental cost-effectiveness ratios for intensive glycemic control – as defined by the United Kingdom Prospective Diabetes Study (UKPDS), mean HbA1c of 7.0% relative to 7.9% (conventional control) – from a health system perspective [20].

The study assumed the intensive glycemic control would be applied to all those in the USA with newly diagnosed type 2 diabetes. This intervention would lead to an undiscounted 0.3173-year increase in life expectancy and a discounted 0.1915-year QALY increase.

Because patients lived longer, the treatment costs increased slightly, but the complications cost dropped by 12%. The incremental total cost was $7927, and the cost-effectiveness ratio was $41,384/QALY (costs were expressed in 1997 US dollars). Cost-effectiveness ratios increased rapidly with age at diagnosis, starting at $9614/QALY for patients aged 25 to 34 years and reaching $2.1 million/QALY for patients aged 85–94 years [20]. These results suggest that intensive glucose control may not be cost-effective in patients who are very old.

Although the CDC analyses provide an important valuation of intensive glucose control, a number of unexplored issues are noteworthy. The CDC analyses and others of that era did not account for hypoglycemia, which can result in serious consequences such as seizures, unconsciousness, or death. Older patients with type 2 diabetes are at particularly high risk for hypoglycemia and its consequences. Accounting for hypoglycemia might very well alter the overall estimate of the clinical benefits of intensive glucose control. Original analyses also did not account for the clinical or preference heterogeneity of older patients. Patients' preferences regarding treatments, particularly the preferences for mode of delivery, are highly variable. When the preferences of individual patients were incorporated into a CUA of intensive glucose control, the ICER for glucose control was highly sensitive to assumptions regarding quality of life with treatments defined as oral medications or insulin [21].

37.6.2 Blood pressure control

The CDC Diabetes Cost-effectiveness Group also compared the cost-effectiveness of intensified hypertension control (treatment with an angiotensin-converting enzyme (ACE) inhibitor or a β-blocker) with a more moderate hypertension control (treatment with diet and drugs but without ACE inhibitors and β-blockers) [20]. In their model, intensified hypertension control affected the probability of stroke and reduced the transition probability for nephropathy and retinopathy. The model only applied intensified hypertension control to people who had hypertension (defined as systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg or by antihypertensive medication use). Average blood pressure levels by age group for people with diabetes were calculated using data from the third National Health and Nutrition Examination Survey (NHANES III). Their findings showed that the cost-effectiveness ratio is −$1959/QALY, which suggests that intensified hypertension control reduces costs and improves health outcomes relative to moderate hypertension control. When stratified by age group, the cost-effectiveness ratios showed cost saving for all age groups except the oldest age group (85–94 years old). Overall, the study found that intensified hypertension control is the most cost-effective, followed by reduction in serum cholesterol level and intensive glycemic control.

37.6.3 Cholesterol level

The CDC Diabetes Cost-effectiveness Group compared pravastatin with no drug treatment for people with a high serum cholesterol level but without a history of coronary heart disease (CHD) [20]. It was assumed in the model that the reduction intervention of serum cholesterol level lowered the probability of CHD and had no effect on the transition probabilities for other complications. The intervention was only applied to people with a high serum cholesterol level, defined as a total serum cholesterol level of 200 mg/dl (5.18 mmol/l) or higher. The NHANES III serum cholesterol level data for people with diabetes was used in the Framingham calculations to determine CHD and stroke risks.

Primary reduction in serum cholesterol level using pravastatin increased undiscounted life expectancy by 0.6722 years and discounted QALYs increased by 0.3475. Standard treatment costs increased slightly as life expectancy increased. The increased life expectancy also led to an increase in complications cost, as the cost of living longer with neuropathy, nephropathy, and retinopathy complications outweighed cost reductions from CHD and stroke. The incremental total cost was $18,033 and the cost-effectiveness ratio was $51,889/QALY. Cost-effectiveness ratios for reduction in serum cholesterol level varied by age, with the lowest cost-effectiveness ratio for patients aged 65–74 years ($40,471/QALY), followed closely by patients aged 55–64 years ($43,331/QALY), patients aged 75–84 years ($51,459/QALY), and patients aged 45–54 years ($52,554/QALY). The cost-effective ratio for patients aged 85–94 years was $110,124/QALY because of limited QALYs gained among this age group, which suggests that efforts in reducing serum cholesterol level may not be worthwhile in patients who are very old.

37.7 Cost-effectiveness of new approaches to care management and coordination of care

One of the most important clinical trials of the past decade is the Look AHEAD (Action for Health in Diabetes) trial, an intervention designed to alter the diet and exercise habits of individuals already living with type 2 diabetes who are also overweight or obese [22, 23]. The trial results are intriguing because patients managed to achieve optimal multifactorial risk factor control and reduce their use of medications through lifestyle changes among patients aged 45–75 years (mean age was approximately 59 years old). The first decade of follow-up of the trial showed that weight loss was greater in the intensive lifestyle intervention group than in the control group throughout the study (8.6% vs 0.7% at 1 year, 6.0% vs 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels. During the approximately 10-year trial period the lifestyle intervention did not reduce the primary outcome of cardiovascular morbidity and mortality [23]. The long-term health and economic consequences of this trial are largely unknown and will be stimulating for public health officials.

Another major development of diabetes care is the arrival of new technology and medical devices to help monitor and deliver treatments. Patients with type 1 diabetes must have insulin delivered by injection or a pump to survive. A continuous glucose monitoring (CGM) trial sponsored by the Juvenile Diabetes Research Foundation found that using a CGM medical device improved glucose control in subgroups of type 1 diabetic patients [24]. The societal-perspective CEA was conducted in trial populations in which CGM had produced a significant glycemic benefit (HbA1c≥7.0% in a cohort of adults aged 25 years or older and HbA1c<7.0% in a cohort of all ages). Trial data were integrated into a simulation model of type 1 diabetes complications. The main outcome was the cost per QALY gained. In-trial CEA showed that CGM patients experienced an immediate quality-of-life benefit (HbA1c≥7.0% cohort: 0.70 quality-adjusted life-weeks (QALWs), $p=0.49$; HbA1c<7.0% cohort: 1.39 QALWs, $p=0.04$) and improved glucose control. In the long term, in the interpretation of the CEA for the HbA1c≥7.0% cohort, CGM was projected to reduce the lifetime probability of microvascular complications; the average gain in QALYs was 0.60. The ICER was $98,679/QALY. For the HbA1c<7.0% cohort, the average gain in QALYs was 1.11. The ICER was $78,943/QALY.

Apart from new therapy and devices, one of the fundamental questions is whether or not care for older patients can be reorganized in order to improve health outcomes and lower costs. A modern diabetes care system for older adults requires a multidimensional approach, including prevention of diabetes and its complications, early detection and intervention for vascular diseases, and evaluation of functional status [25]. Unfortunately, our knowledge relating to diabetes care in older adults is still limited on several fronts: (i) no large-scale interventions studying diabetes care in oldest adults (e.g., persons older than 75 years) are available, (ii) evidence of benefit and harm from intensive glycemic control is limited and inconsistent, (iii) evidence for lipid lowering is limited, (iv) evidence of an optimal diabetes care delivery model is lacking so that no recommendation is available, and (v) little evidence is available to support metabolic or educational interventions for long-term care residents or those who are housebound.

In the USA a number of new care delivery models are being introduced, such as the Patient Centered Medical Home and the Accountable Care Organizations (ACOs). Each of these new models of care should be subjected to a CEA. As an example, an ACO unites groups of physicians, healthcare providers, and hospitals into a virtual coordinated care network. Members of the ACO accept shared responsibility and incentive for reducing the cost and improving the quality of care provided to a given group of patients. In this model, savings that are generated by the ACO are shared with the payer. The ACO receives shared savings only if it can meet standards of quality of care in four areas: patient/caregiver care experiences, care coordination and patient safety, preventive health, and at-risk population health, including diabetes and cardiovascular disease. The Affordable Care Act created the Medicare Shared Savings Program, which is estimated to have saved up to $940 million within the first 4 years.

One of the real frontiers of geriatric diabetes is establishing the evidence base for caring for patients living in long-term care facilities. One-quarter of long-term care

residents are diabetic. These individuals are at an increased risk for hypoglycemia and other complications, including hyperglycemia, depression, falls, infections, and foot wounds. Residents in long-term care facilities often have poor nutritional status and may be volume depleted, both contributing to higher rates of glycemic variability. To date, health policies have not provided adequate support for the many facets of providing comprehensive diabetes care in these settings. Future support for equipping these facilities with appropriately trained healthcare providers and implementing diabetes-related protocols for managing medications and hypo- or hyperglycemia are crucial to providing care for this important sub-population of older adults. Additionally, for chronically ill, home-bound older adults, more programs enabling home health care and visits may help reduce complications and prevent hospitalizations. As these interventions become formally studied, it will be critical to evaluate their economic value using tools such as CEA.

Developing effective interventions to target the multifaceted nature of disabling condition in older adults is a pressing need in geriatric diabetes. The traditional metabolic model of care is no longer sufficient to meet the needs of many patients, let alone older patients. These challenges make geriatric diabetes an area for further research and development, and should be emphasized in the training of all geriatricians, diabetes specialists, and primary care physicians.

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CHAPTER 38
Clinical trials in older people

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KEY MESSAGES

- Interventions can be non-pharmacological, such as introduction of an exercise, education or nutritional program or medical devices, or pharmacological, for the initial approval drugs or new indications for drugs that are currently approved.
- Clinical trial interventions in older people involved in a study require constant monitoring to ensure an optimal and ethical realization.
- The European Medical Agency authorizes approximately 4000 clinical trials each year. This is equal to approximately 8000 clinical-trial applications.
- The optimum choice of research design will depend on the research question to be answered.
- Clinical trials in older people that have too many restrictive criteria will be very difficult to complete and often not represent the real situation.
- Potential strategies to aid the recruitment of older people into clinical trials have been published.

38.1 Overview of clinical trials

Clinical trials are a necessity arising from constant scientific development in response to the needs of the population, giving objective, reproducible, and controlled results under the available clinical evidence.

Clinical trials are studies that aim to discover or verify the effects of one or more clinical intervention in the human population. The interventions are evaluated using appropriate parameters (laboratory scales, clinical outcomes, morbidity among others, etc.) to determine whether or not they are beneficial in the clinical practice. Interventions can be non-pharmacological, such as introduction of an exercise, education or nutritional program or medical devices, or pharmacological, for the initial approval drugs or for new indications for drugs that are currently approved. In the latter studies, the effects of two or more treatments or therapeutic interventions are compared in a homogeneous group of people with similar medical conditions.

Because of the enormous impact that could arise from a clinical trial intervention on the people involved in the study, constant monitoring is required to ensure an optimal and ethical realization. Those responsible for this observation are, in order of action, the ethical committees of each center, the national drug agencies and the European Medical Agency (EMA), which supervises adhesion to the standards of ethical and scientific quality of clinical trials (design, registration, and reports), also known as good clinical practice (GCP). Regardless of where they are conducted, all clinical trials seeking a marketing authorization for human medicines in the European Economic Area must be carried out in accordance with the requirements set out in Annex 1 of Directive 2001/83/EC, fulfilling the legislation (Directive 2001/20/EC), GCP and the Declaration of Helsinki.

The EMA authorizes approximately 4000 clinical trials each year. This is equal to approximately 8000 clinical trial applications. Of these, 61% are sponsored by the pharmaceutical industry and 39% by non-commercial

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sponsors, mainly academia. The regulation of clinical trials aims to ensure that the rights, safety, and wellbeing of trial subjects are protected and the results of the clinical trials are credible.

The right combination of characteristics in the different types of clinical trial allows an ideal clinical trial to be constructed. Although the ideal clinical trial is the one that best suits the conditions of each intervention, the basic pillars are:

- determination of sample origin and size (explain how patients who meet the criteria were selected and why they should or should not participate in the study to produce a homogeneous and accurate representation of the target population)
- random assignment (a way of defining what kind of intervention the patient will receive at random to ensure that the groups compared are statistically equivalent)
- exposure to the comparison control drug (to have a reference group which supports the data)
- masking (procedures that prevent those involved in the study from knowing the group the subject is in to neutralize any bias).

According to the objectives and the information available the following types of clinical trials are distinguished:

Phase I: This is the first step in the investigation and provides preliminary information on the effect and safety of the product in healthy subjects or, in some cases, patients (pediatric, oncologic, etc.). The pillars of phase I trials are the pharmacokinetic and pharmacodynamic aspects.

Phase II: These trials are performed in patients with the clinical condition of interest. They provide preliminary information on the efficacy of the product, establish the dose–response relationship, define the variables used to measure efficiency, and extend the safety data (randomized and controlled).

Phase III: These trials evaluate the efficacy and safety of the experimental treatment with a larger patient sample than in Phase II, trying to reproduce the conditions of normal use and considering the standardized treatment in the studied condition (randomized and controlled).

Phase IV: These studies are performed with drugs in the post-marketing stage. They provide additional information regarding the benefits and risks of treatment in long-term use in clinical practice.

38.2 Clinical trials for older subjects

Because of the overwhelming growth in the geriatric population (from 84 million in 2008 to around 141 million by 2050), the EMA has sounded the alarm on the need for clinical trials in these subjects since there are a number of differences between elderly people and younger people that have a significant impact on their treatment with drugs. The EMA recognizes that it will need to ensure that the needs of the elderly are taken into account during the development, approval, and clinical use of medicines.

The EMA also undertakes the follow-up or pharmacovigilance of medical products once they hit the market, especially of drugs used in the elderly given that they might be at a higher risk of suffering side effects compared to younger patients. Covering this inequality should be a priority to ensure that our increasingly elderly population gain access to information and high-quality clinical care.

Because of the special characteristics of elderly patients (both pharmacokinetic and pharmacodynamic), the prevalence of clinical trials in this population segment is low, but has seen a steady increase in recent years.

A review of the literature on currently active randomized clinical trials in humans revealed a total of 377,072 articles. However, when the same search is repeated with elderly being given as a parameter, and specifically diabetic patients, 412 results were obtained (see Figure 38.1).

The search illustrated in Figure 38.1 was carried out in PUBMED, looking for clinical trials in elderly diabetic patients, on 31 January 2015, using “diabetes” as the major term, “elderly” in its different MESH terms, and “clinical trials”. We used the following sequence:

#1 “diabetes mellitus”[MAJR]

#2 (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) OR systematic[sb]“Clinical Trial”[Publication Type]

#3 “Aged”[Mesh]

#4 #1 AND #2 AND #3

#5 (geriatr* OR elder* OR older OR “senior citizen” OR “senior citizens” OR retired OR retirement OR Retiree* OR “social security” OR “nursing home” OR “assisted living” OR “nursing home” OR “nursing homes” OR pension* OR senil* OR dementia OR grandparent* OR grandmother* OR grandfather* OR grandma* OR grandpa* OR septuagenarian* OR octagenarian* OR

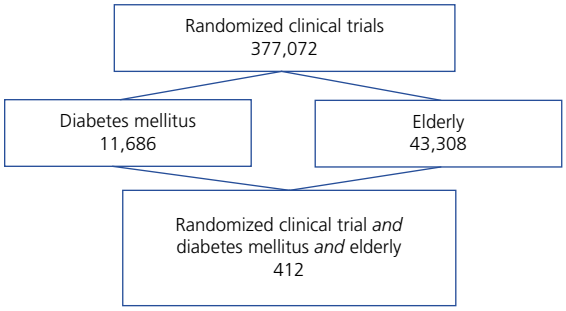

Figure 38.1 The search strategy for clinical trials.

sexagenarian* OR nonagenarian* OR centenarian* OR supercentenarian*) AND (aged[mesh] OR elderly[TI] OR AGED[TI] OR SENIOR[TI] OR "aged, 80 and over")
#6 #4 AND #5

As shown in Figure 38.1 this search produced 412 studies. The time period of the publications was from June 1984 to September 2014 (30 years). The results included different types of studies:

- clinical trials with drugs (effects and safety)
- clinical trials comparing two drugs
- educational intervention programs (exercise, nutrition, supplements to diet, etc.)
- descriptive studies
- adherence to treatment studies
- telemedicine
- economic analysis
- others.

From the search it can be seen how the number of clinical trials has increased in recent years and how the type of trial has changed. For example, between 1984 and 1991 (7 years) only 12 studies were published, most of them (8) related to drugs and only 3 with educational intervention programs. The remaining study was related to adherence to the treatment.

In contrast, in the last 4 years (2011–2014) 96 studies have been published, with a change also in the type of study. Currently clinical trials are mainly educational intervention programs, primarily exercise programs and to a lesser degree nutritional interventions or drug trials (Table 38.1).

The results listed by study type are:

- clinical trials with drugs (effects and safety): 159
- clinical trials comparing two drugs: 27
- educational intervention programs (exercise, nutrition, supplements in diet, etc.): 110
- descriptive studies: 58
- adherence to treatment studies: 3
- telemedicine: 25
- economic analysis: 4
- others: 26

From this review it can be seen that there has been an increase in the total number of clinical trials focused on the elderly. Twenty or 30 years ago the most common clinical trials were related to pharmacology, but more recently the focus has been on educational intervention programs. The complex conditions found in the elderly (both pharmacokinetic and pharmacodynamic) drive clinicians towards more educational programs and away from pharmacological interventions, not just to avoid the possibility of adverse reactions but to improve adherence.

38.3 Differential aspects of clinical trials in elderly subjects

Until recently, elderly people, especially the frail and the very old, tended to be excluded from randomized controlled trials (RCTs), usually without justification. Yet the RCT is widely acknowledged as the 'gold standard' experimental design in clinical medicine and, given the disproportionate burden of disease and use of health and social care resources by older people, it would seem especially important that they should be included in clinical trials in significant numbers. Indeed, in many indications it is older people who represent the majority of the patient population.

People older than 65 represent about 14% of the population in most industrialized countries, and constitute nearly one-third of global medication consumers. Extensive evidence indicates that even in healthy older people aging affects the way the body responds to medication.

The EU population will grow older because people are living longer and the birth rate is declining. The median age of the EU population is expected to rise from 41 years in 2010 to 48 years in 2060. By 2060 people aged 65 or older will account for about 30% of the EU population. However, poor health does not have to be an inevitable consequence of aging. Older adults who engage in healthy behavior, take advantage of clinical preventive services, and continue to interact with family and friends are more likely to remain healthy, live independently, and incur fewer health-related costs.

Table 38.1 Description of publications by groups of 100 articles.

Type of study	Study period (per 100 studies)				
	(1984–1992) 8 years 12 studies	(1992–2003) 9 years	(2003–2009) 6 years	(2009–2011) 2 years	(2011–2014) 3 years
Clinical trials with drugs (effects and safety)	4	46	47	18	44
Clinical trials comparing two drugs	4	11	6	5	1
Descriptive studies	0	14	10	22	12
Educational intervention programs	3	22	22	31	32
Adherence to the treatment	1	1	1	0	0
Telemedicine	0	2	7	11	5
Economic analysis	0	0	2	2	0
Others	0	4	5	11	6

The largest costs in the development of a drug occur in the pre-market phase. From a statistical point of view, increasing the variability by including heterogeneous patients, such as elderly patients, results in a considerable increase in sample size to achieve adequate power. It is therefore not surprising that those who design RCTs are reluctant to include elderly patients.

Aging involves a number of associated issues that make choosing a treatment difficult. Lack of scientific evidence, physiological alterations, inappropriate medication, and polytherapy can all lead to adverse reactions.

All pharmacological treatments involve a number of known and unknown risks which must be less than the expected benefit for the drug to be effective. With aging this benefit–risk rate is much more difficult to calculate because older people (75 years or older) take more drugs than younger adults and therefore it is difficult to calculate the risk due to each medication.

Reasons given for excluding older people from RCTs include concerns about gaining consent, protocol eligibility criteria with restrictions on co-morbidities and concomitant medications, worries about poor compliance and high attrition, and fears of an unacceptable level of adverse events. Most of these concerns are unfounded or can be easily overcome. Ethical unease about experimenting on elderly people, who are considered "vulnerable" on the sole basis of their age, is also sometimes cited. This reflects the misguided paternalism of younger researchers and relatives, ignoring the older person's right to autonomous decision making.

As a possible solution, the following proposals are described in the literature:

- Legislation can and should be brought forward to ensure that older people are adequately represented in clinical trials.
- Along with this legislation, changes must be made to the regulatory control frameworks for pharmaceutical and medical device licenses. It should not be possible for new licenses to be granted unless there is evidence of efficacy in the population for which the prescription is intended.
- The research team must have experience in caring for older people, not only for interviewing and signing the informed consent, but also in setting the agenda for visits, and planning and conducting the test. The participation of geriatricians and nurses with expertise in the care of the elderly is essential to ensure the representation of older people in RCTs.
- An ethical approach to research is to ensure that the benefits are available to all patients equally. Ethics committees must therefore ensure that older people are included in clinical trials, and do not allow protocols to unfairly exclude older people because of age co-morbidities.

It is very important to establish the differences between performing clinical trials in young adults

and in older adults. The main differences are described in detail in the following sections.

38.3.1 Clinical trial design

The optimum choice of research design will depend on the research question to be answered. Only experimental studies can provide reliable evidence of causality and a RCT is the research methodology of choice to examine the effectiveness and safety of an intervention in the clinical setting.

It is necessary to perform clinical trials in the elderly population in all the phases to establish safety and effectiveness in this group.

In Phase I trials, the study drug or agent is tested in a small group of subjects (20–80) in single ascending dose (SAD) and multiple ascending dose (MAD) studies to assess a safe dosage range, the best method of administration, and the tolerance and safety (pharmacovigilance). The results in clinical trials performed in young adults should not be extrapolated to older adults.

In Phase II trials, the study drug or agent is given to a larger group of subjects (100–300), generally patients with the study indication, to further assess safety and dosing requirements (Phase IIA) and to undertake preliminary studies of efficacy (Phase IIB). Specific trials focused on elderly patients may be useful as they constitute the majority of the population of patients consuming drugs and therefore regulatory authorities should require Phase II clinical trials in people older than 70 years before marketing.

In Phase III the effectiveness and safety of the drug are evaluated. Inclusion and exclusion criteria based only on age should be not allowed in this phase because they are unjustified.

Phase IV (post-marketing) trials are designed to provide additional information about the long-term benefits and risks of treatment in clinical practice. Serious adverse effects identified at this late stage in elderly patients have resulted in the withdrawal or restricted use of several prominent drugs.

The study design should include:

- ethics and justification
- the susceptible population to be included
- the selection of patients and consent forms
- the randomization process
- a detailed description of the intervention
- comprehensive monitoring, including losses and non-compliance
- measuring the final variable
- comparison of results between the intervention and control groups.

Special note should be taken of the inclusion and exclusion criteria. These criteria must be selective but not restrictive. Clinical trials in older people with too many restrictive criteria, will be very difficult to complete, and will not represent the real situation. These criteria should identify the target population for each area of research. If measures are not realistic for clinical practice in the studied population, the trial outcomes will not be applicable in the real world. Extensive lists of inclusion and exclusion criteria may exclude those with other co-morbidities or taking other medication and the resulting trial population can end up bearing little resemblance to patients normally presenting in the clinic.

It is very important that all groups are represented in the sample. Those older than 65 years should be stratified by age (65–75, 75–85, and >85 years) so that they represent all subpopulations. Stratified randomization can be used to ensure particular groups (e.g., the very old) are evenly distributed.

38.3.2 Recruitment

Recruiting a sufficient number of participants in a clinical trial at the right time is a major challenge for researchers.

The method of recruitment has a big impact on the motivation of the participants, and is particularly relevant in the case of elderly patients. It is very important to respect the principle of autonomy. We are used to treating elderly subjects as a vulnerable population but we must take into account that this population is not vulnerable and they are able to take their own decisions in an autonomous way. Elderly people are not particularly pro-active in finding out about clinical trials to participate in. Participation should be offered and the details of the trial explained rather than taking a decision on behalf of the older person. Older research participants are more motivated than the young by feelings of altruism and "paying back" those who treat them and are less concerned about financial compensation for volunteering. A systematic review of factors that limit the quality, number, and progress of RCTs (in all age groups) identified many clinician- and patient-based barriers to participation. Clinician barriers included time constraints, lack of staff and training, worry about the

Table 38.2 Possible strategies to improve the participation of older people in clinical trials.

Commissioners and ethics committees
Eligibility criteria in clinical trials to be justified by trial designers
Trial design
Minimization of exclusion criteria
Inclusion of patient preference arm
Larger sample size
Involvement of clinical staff in research design and implementation
Simplified protocols
Minimal demands on clinical and support staff
On-site coordination by clinical staff
Employment of data manager, age/sex registers, and good tracking system
Training for research staff
Conduct trials in well-established clinical settings
Comprehensive geriatric assessment
Recruitment process
Recruitment by specialized research staff, principal investigator, general practitioner, specialist clinic, older people or research nurse
Recognition and understanding of the culture of different ethnic groups
Mass marketing and advertising
Postal and telephone two-step strategy
Community outreach, health fairs, lectures
Personalized and face-to-face recruitment
Initial communication with trusted professional to establish the credibility of the study
Emphasis on the benefits of participation to others
Make expectations clear at initial contact
Easy physical access to research institutions
Provide transport or help arrange lifts, reimburse transport costs and parking
Offer home visit
Allow sufficient study time
Extended patient recruitment period
Financial incentives
Trial conduct (adherence)
Be alert and responsive to potential signs of drop-out and solve any problems
Reminders of commitment, reiterate motivations, emphasize need for complete data
Minimize respondent burden and give control to participants
Give instrumental or tangible support

Table 38.2 (Continued)

Enlist support from relatives, friends, physician and healthcare professionals
Establish the best time to call, including evenings and weekends, flexibility
Schedule study visits to coincide with other appointments (e.g., outpatient clinics)
Frequent follow-up and contact
Individualized number of contacts if perceived as too much of a burden
Reminder letters prior to visit
Home assessment visits
Offer phone/postal/e-mail/surrogate follow up and pay postage costs
Provide incentives or small tokens of appreciation, study specific items
Birthday/Christmas/thank you/illness cards
Newsletters/feedback on study

impact on the doctor–patient relationship, concern for patients, loss of professional autonomy, difficulty with the consent procedure, lack of rewards and recognition, and an insufficiently interesting question. Patient barriers included additional demands of the trial, patient preferences, worry caused by uncertainty, and concerns about information and consent. The PREDICT study identified a range of possible interventions to improve recruitment (Table 38.2).

Efficiency in the recruiting process mainly depends on the methods used by researchers to recruit subjects, the potential advantages and disadvantages of the tested drug or intervention, and the burden of study procedures. In general, this efficiency decreases with increasing age of the subjects. Investigators should explain the clinical trial because they understand the detail of it. It is useful to recruit partners (husband and wife) or people who live at the same address, but this can result in selection bias.

The best option to improve the recruitment procedure is to introduce only the selection criteria mandatory for the project and try to balance the overload for participating with the benefits to be obtained, both economically and at other levels. Additionally, older people may need transport support as caregivers (relatives, neighbors, etc.) may be working and not able to help. Empowerment of elderly subjects to take their own decisions is the right way to proceed.

The sample size may need to be increased because of these difficulties and withdrawals.

38.3.3 Informed consent

Seeking truly informed and freely given consent is fundamental to all research involving human subjects, but an assumption that decision-making capacity is likely to be impaired in older people and a misguided paternalism to protect the "vulnerable elderly" should not act as a barrier to their participation in clinical trials. Certainly the research participant must be able to retain and understand the relevant facts explained to them, be allowed sufficient time to weigh up benefits and risks to make a choice (without coercion), and then to communicate their decision to the researcher. Informed consent must contain the correct and necessary information:

- diagnosis
- treatments available
- investigational treatment
- potential risks and benefits of treatment
- concept of the clinical trial (CT) (design, use of placebo, etc.)
- discomfort associated with the EC
- follow-up visits involved participation in the EC.

Obtaining consent should not be seen as a bureaucratic exercise, but as an essential part of the EC that requires time, insight, and communication skills.

Informed consent should be obtained by a person on the research team, and time taken to ensure that the patient and/or companion has understood the essence of the study and its procedures. If possible, consent should be obtained by the geriatrician responsible for the patient or the physician responsible for the study.

Unfortunately, the growing regulatory burden on research has tended to make the consent process less effective, with information sheets written to address legal issues and too often expressed in detailed language that is difficult to understand, obscuring basic issues and defeating the ethical purpose of the informed consent process. Information sheets should be written in colloquial language understandable by the people to whom they are addressed. Whilst older people may have more difficulty comprehending consent information than those who are younger, this appears to be due to education differences rather than age itself. Particular attention should be given to compensating for communication and sensory deficits, and to improving the readability of information sheets and consent forms. It is a mistake to consider elderly people as vulnerable only because of their age. This could be a violation of the autonomy principle.

38.3.4 Retention

As important as recruitment is the retention of subjects in clinical trials. It is important to try to avoid withdrawals and loss of follow-up. To achieve this, action can be taken to maintain a high level of communication by facilitating good access to the investigator team and keeping participants informed about the study progress by sending newsletters. Reminders about forthcoming visits can be provided by means of calendars, fridge magnets, phone calls, etc.

Comfortable waiting spaces at hospitals or clinics and parking/transport services can be a good way to improve retention. It can be beneficial to provide spaces without barriers at hospitals to avoid falls and unnecessary effort.

Elderly subjects usually are accompanied to their appointments by their caregivers. Informal caregivers can be relatives, neighbors, or friends. They may have to miss work or take time away from other tasks to accompany the participant, so the availability of the caregiver must also be taken into account. Reducing the number of visits, shortening waiting times, and making home visits will improve the performance of the trial and reduce the dropout rate.

A formal "thank you" when the study ends and feedback about the final outcome is appreciated and expected.

38.3.5 Outcomes

As well as the standard outcome measures of morbidity and mortality, RCTs in older people commonly need to consider broader issues that impact on quality of life, especially functional, cognitive, and social outcomes.

Chosen measurement instruments must be valid (recording the attribute that they purport to measure), reliable (recording consistent results under varying conditions of measurement), and responsive (able to detect change). Other factors to be considered when selecting an instrument are whether it is self-administered or researcher-administered. Self-administered questionnaires should be easy to complete and not too long. Support should also be given for any disabilities. The style of these questionnaires must be easy to follow.

The lack of validation of standardized measurement instruments for use in elderly populations is a problem. We cannot use questionnaires validated in young people for elderly people. The scales must be adapted to the heterogeneity of the elderly population. Experience with measures in younger, fit subjects cannot reliably be extrapolated to older patients with their higher prevalence of mobility impairment, frailty, and pre-frail status, and institutionalized, sensory, and communication deficits. Certainly all assessors need to be trained to ensure consistency (inter- and intra-rater reliability) and help to minimize bias.

38.3.6 MID Frail: Paradigm

One of the most important projects in older people with diabetes is still being carried out in Europe, funded by the European Commission under the 7th Framework Program.

The MID-Frail study project focuses on the use of interventions designed to improve functional status and enhance quality of life rather than traditional treatments such as glucose and blood pressure lowering by acting on the mechanisms involved in producing frailty and its progression to adverse outcomes. This is justified for several reasons. First, there has been a marked lack of intervention studies in older people with diabetes. Second, current clinical guidelines appear to be of limited utility in these patients, and, third, improvements in function and wellbeing may be fundamentally of more clinical benefit in older frail patients with diabetes than attention to metabolic control alone. These facts, coupled with increasing concerns over the detrimental effects of aggressive glucose lowering in type 2 diabetes, provide a significant platform for addressing non-metabolic control areas to improve clinical outcomes. The severity of the long-term impact of diabetes in an aging population in terms of excessive healthcare expenditure serves to further support the value that may derive from this project.

The MID-Frail project includes the main changes and aspects to take into account in clinical trials in older people.

The main objective is to evaluate the effectiveness of a multimodal intervention in frail and pre-frail subjects aged ≥70 years with type 2 diabetes in terms of function and quality of life in comparison with usual clinical practice.

The secondary objectives are:

1 To evaluate, in comparison with usual clinical practice, the effectiveness of a multimodal intervention in any of the following: (i) economic costs/healthcare expenditure due to diabetes, (ii) the incidence rate of symptomatic hypoglycemia and hypoglycemic coma, (iii) the incidence of hospital admission, (iv) the incidence of permanent institutionalization, and (v) the carer burden.
2 To evaluate the mechanisms underlying the effects of the intervention by (i) studying changes in body composition with exercise (SARTRAIN SubStudy) and the effect of increased power in both isometric and dynamic actions (MID-POW SubStudy) and (ii) studying the role of metabolome (MetaboFrail SubStudy) and genetic polymorphisms (GeneFrail SubStudy) as determinants of the response to treatment.
3 To evaluate the efficacy of new therapeutic devices (SENSOLE SubStudy) and new ways to measure changes in quality of life (QoLFrail SubStudy).

The multimodal intervention consists of the following:

- optimization of glycemic and blood pressure control to obtain the target for glycemia: optimal HbA1c range of 7–8% (9.6–11.6 mmol/l) and blood pressure set in an optimal range of <150/90 mmHg
- an educational and nutritional program for the nutritional and diabetes educational intervention for the MID-Frail study has been designed which has been adapted to meet the needs of a population of older people with diabetes
- a physical exercise program.

The quality of life and the maintenance of function are the main objectives in clinical trials focused on elderly people.

38.3.7 MID Frail: Design

Special attention has paid to the design of the study. It is an open-label randomized multicenter study, with random allocation by clusters to the usual care group (UCG) or the intervention group (IG). The randomization unit is the cluster to avoid or control for contamination bias. Every trial site (TS) has a mean average size of 14–15 subjects. Every national research center (RC) is in charge of 11–12 TSs. The total duration of participation for each subject is approximately 108 weeks. Signed informed consent for patients and caregivers is required before any study procedures are carried out.

The main inclusion criteria are for participants to be aged 70 years or older, with a diagnosis of type 2 diabetes for at least 2 years, and fulfilling Fried´s criteria for frail or pre-frail individuals.

Additionally, particular attention has been given to caregivers. An information sheet and informed consent form were designed specifically for caregivers in addition to the participant information sheet. The evaluation of the quality of life of caregivers is one of the objectives of the MID Frail project.

To improve participant retention, only essential visits are made. Transport support was offered to participants to facilitate attendance.

Comfortable spaces to perform the exercise and educational sessions were provided. Additionally, posters with pictures and direct messages were designed for the educational sessions. All the documents for the participants were written in colloquial language adapted to the knowledge of the participants. Specific personnel with experience with elderly people were responsible for the recruitment.

Taking into account that elderly subjects have high comorbidity, it was established that the exclusion and inclusion criteria were not too restrictive to recruit participants who were representative of the general population.

The targets for HbA1c and blood pressure were not too restrictive and the design respects the European guidelines for older and frail people with diabetes.

This study exemplifies the paradigm of a clinical trial in older people with diabetes.

Further reading

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