Prevalence and Correlates of Hypovitaminosis D in Children and Adolescents with Sickle Cell Disease

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Abstract

Hypovitaminosis D is associated with a variety of health conditions. Understanding the effects of low vitamin D levels on children and adolescents with sickle cell disease (SCD) remain limited. The project's aim was to determine hypovitaminosis D prevalence in children and adolescents with SCD and explore correlates to improve current screening and treatment strategies. A retrospective, electronic health record (EHR) review was conducted on 104 children and adolescents with SCD who attended a non-profit tertiary children's hospital in southwestern Pennsylvania. A descriptive, cross-sectional, correlational design was used to examine hypovitaminosis D prevalence and correlate vitamin D levels with comorbidities, medications, biological and environmental factors in this sample. Results demonstrated the hypovitaminosis D prevalence rate was 88.5% (< 30 ng/mL); deficiency occurred among 39% (< 20 ng/mL); subjects were 6.9 times as likely to have lower vitamin D levels in fall versus summer ($p = 0.0007$). Underweight subjects were 6.2 times ($p = 0.0056$) as likely to have lower vitamin D levels compared to healthy weight subjects. Sufficient vitamin D levels only occurred among subjects ≤ 10. Higher probability of hypovitaminosis D was noted in subjects reporting liking milk "sometimes" versus "yes" ($p = 0.0001$). Hospitalizations for acute chest syndrome (ACS) had an association with vitamin D severity ($p = 0.0497$). The conclusion is hypovitaminosis D is prevalent among children and adolescents with SCD living in southwestern Pennsylvania. To promote future positive patient outcomes, continued identification of correlates associated with hypovitaminosis D will assist in developing well-designed prevention and treatment programs.

Chapter 1

Introduction

Background of problem

Hypovitaminosis D is a condition that results from a spectrum of low circulating levels of vitamin D including: vitamin D insufficiency (VDI), vitamin D deficiency (VDD) and severe vitamin D deficiency (SVD). Hypovitaminosis D is now considered a worldwide health problem even in areas with abundant sunshine (Korchia et al., 2013). Recent studies have concluded that the incidence of hypovitaminosis D may be increasing in the United States (Ginde, Liu, & Carmargo, 2009) and is a common problem among many children and adults (Holick, 2009). Most experts agree that an inadequate vitamin D status is widespread among persons who are in ill health and healthy individuals alike (Moore & Kiebzak, 2007). Therefore a standard of practice for prevention, screening and treatment of hypovitaminosis D in early childhood may obviate future health consequences.

VDD corresponds to a circulating 25-hydroxyvitamin D level of less than 20 ng/mL and may be associated with risk factors in the development of chronic illness across the life span. VDD is commonly found in pediatric patients with sickle cell disease (Buison et al., 2004; Rovner et al., 2008) and although sickle cell disease (SCD) affects many ethnic groups worldwide, in the United States (U.S.) it primarily affects persons of African American descent (Center for Disease Control and Prevention [CDC], 2011). African Americans with SCD have a unique risk for VDD because darker skin types necessitate longer exposure to sunlight to increase circulating vitamin D_3 (Holick, 2004). In addition, patients with SCD are known to have poor weight status which may lead to VDD. Researchers have reported that one quarter of the children among their cohort with more severe forms of SCD exhibited growth failure in their weight percentiles (Zemel, Kawchak, Ohene-Frempong, Schall & Stallings, 2007).

In the U.S. today, milk, some juices, breakfast cereals, breads, yogurts, margarines, and cheeses are fortified with vitamin D in governmental authorized established quantities (Holden, Lemar & Exler, 2008; Holick & Chen, 2008) because naturally occurring vitamin D is limited among other food sources (Holick, 2004). To meet the daily requirements of vitamin D, approximately sixty percent needs to be obtained from these fortified food sources, however, individuals with SCD may be consuming these products in lesser amounts (Calvo & Whiting, 2013), placing them at risk for hypovitaminosis D.

Severe hypovitaminosis D initiates a broad spectrum of bone diseases among healthy children and adults (Holick 2004). In patients with SCD, the skeletal system is particularly vulnerable (Chapelon et al., 2009), and hypovitaminosis D may potentiate underlying bone issues. For example, recurrent pain crisis episodes can result in repeated bony infarctions, and SCD patients are at risk for developing bone infections which are most frequently caused by encapsulated organisms that may lead to chronic bone damage (Chapelon et al., 2009).

Hypovitaminosis D has also been linked to other important co-morbid risk factors in children with SCD, such as asthma (Forrest & Stuhldreher, 2011), decreased pulmonary function (Jackson, Krauss, Debaun, Strunk & Arbalez, 2012), and poorer response to inhaled corticosteroid treatment (Wu, Tantisira, Fuhlbrigge, Weiss & Litonjua, 2012). Pulmonary complications are the second most common cause of hospitalizations among individuals with SCD (Hostyn, de Carvalho, Johnston, & Braga, 2013) and attributed to a higher risk of morbidity and mortality (Knight-Madden, Forrester, Lowes, & Greenough, 2005). Therefore, vitamin D supplementation may be an effective adjunctive to preventing poorer health outcomes in children with SCD.

Current research suggests that hypovitaminosis D may be an associated factor in a variety of health disorders, but despite this evidence, this condition remains under diagnosed and therefore, undertreated (Osunkwo et al., 2011). Further investigation is warranted to identify the connection between hypovitaminosis D and the impact on chronic health conditions, such as SCD, so that appropriate prevention intervention strategies can be initiated (Jackson et al., 2012).

Purpose

The purpose of this quantitative, cross-sectional, descriptive correlational project was to identify the prevalence of hypovitaminosis D, including the subcategories of VDI, VDD, and SVD, among children and adolescents with SCD. Additionally, a retrospective EHR review was utilized to determine if patient's biological traits, environmental factors, medication response, and disease co-morbidities had an association with their vitamin D level.

The specific aims of the study were to:

1. Identify the prevalence of hypovitaminosis D and its subgroups among children and adolescents ages 1 to 20 years of age who attended a non-profit tertiary children's hospital in southwestern Pennsylvania (PA).
2. Identify correlates that influenced vitamin D levels:
    - Biological factors: sickle cell genotype, gender, age, body mass index (BMI), skin type, and milk preference
    - Environmental factors: season and population density according to zip code status
3. Examine the relationship between vitamin D levels and medication response to:
    - Inhaled corticosteroid for asthma treatment, and previously prescribed vitamin D supplementation
4. Investigate the association between hypovitaminosis D and co-morbidities
    - Hospitalizations for acute chest syndrome (ACS) and pain crisis

Research Questions

The research questions answered by this study were:

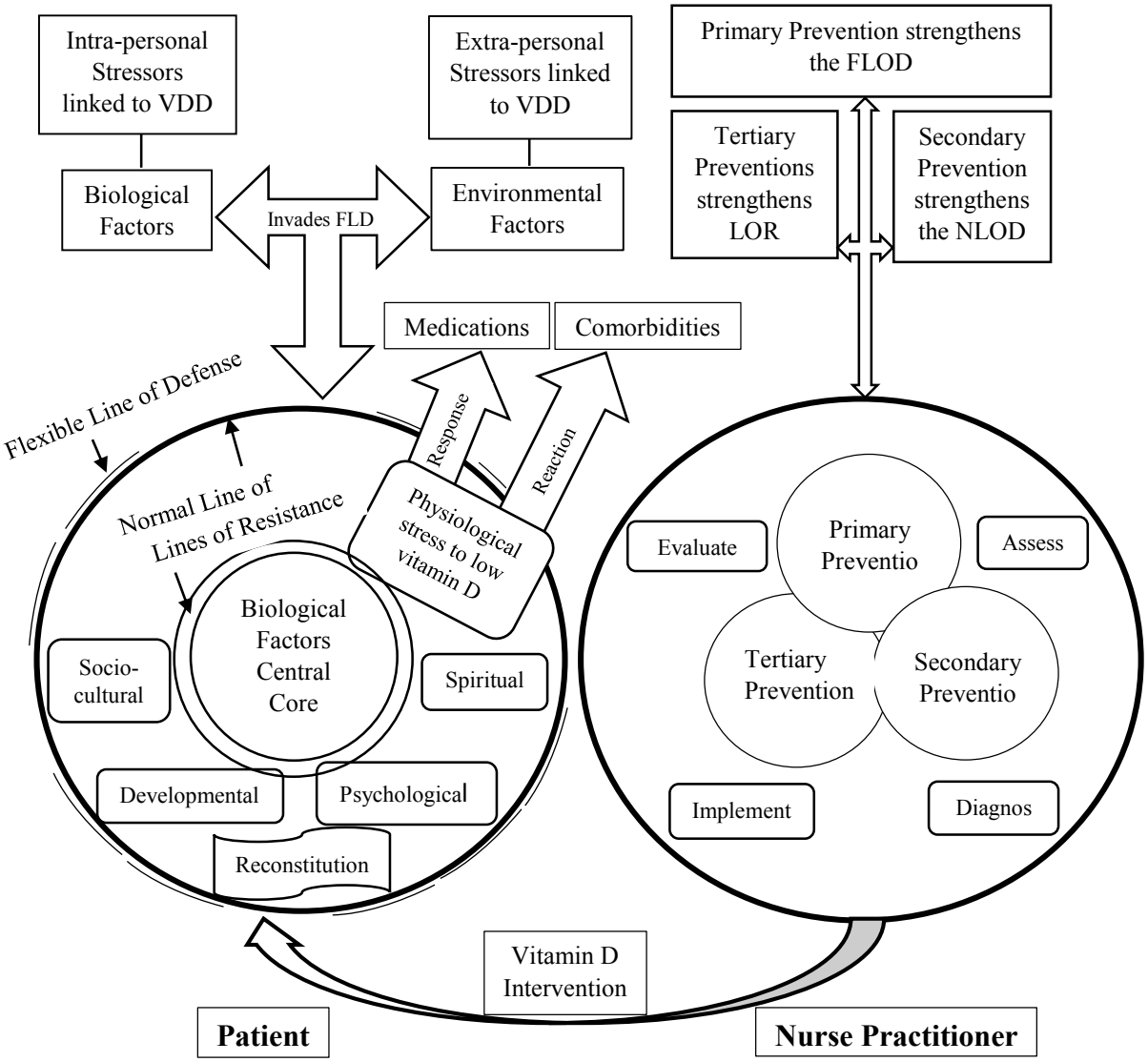
1. Among children and adolescents with SCD what is the prevalence of Hypovitaminosis D including its subgroups?
2. What are the factors associated with hypovitaminosis D (biological, environmental, medications, and comorbidities)?
3. Is there a relationship among the factors that influence hypovitaminosis D?
4. Is there a relationship between hypovitaminosis D that influence co morbidities?

Theoretical Framework

Originally developed in 1970, the Neuman system's model (NSM) was designed as an educational healthcare systems model with an intended use of being beneficial to many professionals in the healthcare field (Neuman & Reed, 2007). The NSM is based on systems theory and posits that the individual is a system that is in continuous interaction with intra-, inter-, and extra-personal phenomena known as environmental stressors that can be either actual or potential (Neuman, 1996). These stressors may invasively disrupt the normal line of defense (baseline state of health) unless the flexible line of defense can initiate compensatory effects through the individual's five system constructs referred as physiological, developmental, psychological, sociocultural, and spiritual (Skalski, DiGerolamo, & Gigliotti, 2006). If the normal line of defense is invaded due to a weakened flexible line of defense, a stressor response will occur (Gigliotti, 2012). In an effort to prevent a severe health consequence, the lines of resistance may be activated to oppose the stressor (Skalski et al., 2006). The goal of the nurse is to reduce severe health outcomes by assisting individuals to strengthen their lines of defense through disease prevention and health promotion strategies (Skalski et al., 2006). Therefore, the NSM may provide a suitable framework to assess the correlation between hypovitaminosis D

and the physiological variable as it relates to children and adolescents with SCD. Figure 1 is an adaption of NSM of primary, secondary, and tertiary prevention intervention.

Figure 1. Neuman Systems Model for Patients with SCD and Hypovitaminosis



Adapted from Gavan, C.A., Hastings-Tolsma, M.T. and Troyan, P.J. (1988). Explication of Neumans' model: A holistic Systems approach to nutrition for health promotion in the life process. *Holistic Nursing Practice, 3(1*), 26-38

The NSM's prevention as intervention has been recognized as a middle-ranged theory (August-Brady, 2000). Published research using NSM has guided a variety of study designs, from quantitative experiments which tested the outcomes of prevention as intervention to qualitative projects have described relevant phenomena (Neuman, 1996). The NSM affords

clarity for the researcher whose interest is guided by the phenomenon of stressors, for example, those attempting to elucidate the relationship between stressors and their relative reactions (Fawcett & Gigliotti, 2001). Other areas of interest in nursing that have employed the NSM have examined such areas as nutritional status across the life span, birth control counseling, prevention interventions for cardio-vascular risk reduction, pain management, culture assessment, and in diverse in-patient and out-patient settings (Neuman, 1996).

The NSM is compatible with today's societal expectancies of nursing practice (Butts & Rich, 2011), as a greater emphasis is being placed on prevention and health promotion strategies. NSM's recognition of the importance of primary prevention has been tested through regulating environmental factors and eradicating predisposing factors (Butts & Rich, 2011). Secondary prevention can be accomplished through early screening and detection of high-risk groups and linking them into specialty healthcare systems. Finally, tertiary prevention includes reducing disability limitations and supporting rehabilitation and other therapies (Butts & Rich, 2011).

In using the NSM, this project investigated the associations between vitamin D levels and the basic or core structure components which include the following biological factors: (a) Sickle cell genotype, (b) Gender, (c) Age, (d) BMI, (e) Skin type, and (f) milk preference. The NSM was also used to examine the association between vitamin D levels and the intra-personal stressors included the following common SCD-related comorbidities: (a) ACS episodes, and (b) vaso-occlusive (VOC) crisis admissions. Additionally, vitamin D levels were evaluated for any associations with extra-personal stressors including: (a) season of the year, and (b) population density according to zip code status. Finally, the association between vitamin D levels and lines of resistance as represented by the following medications were assessed: (a) inhaled corticosteroid strength, and (b) vitamin D supplementation.

The lines of resistance correlate with a person's internal reserves that will affect the degree of reaction to a stressor (Current Nursing, 2012). Children and adolescents with SCD are already reacting to intra-personal stressors and a weakened core structure due to the complexity of their chronic illness. Because their physiological variable is marginalized at baseline, it is important for the nurse practitioner to identify any additional stressors so that appropriate intervention can take place thereby strengthening the lines of resistance.

In patients found to have low levels of vitamin D, invasion of the normal line of defense is thought to have occurred. Depending on a patient's internal reserves, lower levels of vitamin D may be associated with more intrapersonal stressors such as pulmonary complications or pain crisis. Similarly, poorer internal reserves related to suboptimal vitamin D may influence reduced response to inhaled corticosteroids for asthma treatment, thereby necessitating a higher dosing requirement.

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for patients with SCD, though few are adequate candidates due to inadequately matched donors (Mentzer, Heller, Pearly, Hackney & Vichinsky, 1994). However, HSCT is associated with multiple acute and chronic life-threatening complications (Shenoy, 2013). Therefore, the nurse practitioner's role should be aimed at preventing further stressors to the individual. To promote positive outcomes, this project utilized a lines of resistance evaluation that was directed at assessing the patient's vitamin D status (physiological variable), correlating their vitamin D level with the individual's core components, intra-personal environment, extra-personal environment and responses to medications. To mobilize the sickle cell patient toward reconstitution, the nurse practitioner must first employ a vitamin D screening program at the secondary or tertiary

prevention levels to be able to diagnose hypovitaminosis D, initiate treatment if needed, and to continue to evaluate their status as the patient's health is restored to baseline.

Definition of Terms

Hypovitaminosis D-refers to inadequate amounts of the circulating fat soluble vitamin D as measured by the serum biomarker 25 hydroxyvitamin D [25(OH) D], (National Institutes of Health [NIH], 2014) . The total vitamin D is the sum of vitamin D3 and vitamin D2 (Rovner et al., 2008). Vitamin D3 is converted in the body when the skin is exposed to sunlight, it is also found in fortified foods, a few naturally occurring foods in small amounts (e.g., fatty fish, beef liver, egg yolks, and cheese) and vitamin supplements. Vitamin D2 can be found in very few plant based foods in variable amounts (e.g., mushrooms and soy), and vitamin supplements (NIH, 2011).

There are 3 recognized sub categories of hypovitaminosis D that include: vitamin D insufficiency which occurs when hydroxyvitamin D levels are less than 30 ng/mL, vitamin D deficiency that occurs when vitamin D biomarkers drop below 20 ng/mL and severe deficiency when vitamin D levels fall below 10 ng/mL (Holick, 2007).

Sickle cell disease-is a group of inherited blood disorders affecting primarily African Americans that are characterized by abnormal red blood cells that assume a crescent shape which can disrupt blood flow (NIH, 2012).

Biological Factors.

Sickle cell genotypes-is an autosomal recessive condition (American Academy of Pediatrics, 2001). The four most common genotypes are sickle-hemoglobin SS disease (Hgb SS), sickle-hemoglobin C disease (Hgb SC), sickle beta-plus-thalassemia (HgbS/β^{+}), and sickle beta-zero-thalassemia (HgbS/β^{0}).

Gender, Age and BMI- are the patient's demographic and physiologic characteristics.

Skin Type-are the skin tones assessed by Fitzpatrick's Scale (1988) and HTetronics visual chart (2011).

Milk Preference-was the patient's response to the question, "Do you like milk?" The answer was recorded as yes, no, or sometimes.

Co-morbid Conditions-are the presence of one or more disorders that occur simultaneously (NIH, 2010) such pulmonary complications (ACS) and pain syndromes (VOC) identified by a retrospective EHR review for five years.

Environmental Factors.

Seasons-were categorized by the following: spring, summer, fall and winter.

Population Density According to Residence-was categorized according to the U.S. Census. Bureau's (2014) definition of an urban area which comprises 1,000 people per square mile, and a rural setting which includes less than 1,000 people per square mile.

Medications.

Inhaled Corticosteroids (ICS)-are used to control mild, moderate to severe asthma symptoms and are effective treatment intended to inhibit inflammation (NIH, 2013). ICS are prescribed according to asthma severity. Medication doses were recorded during the retrospective EHR review at the time of the vitamin D screening.

Vitamin D Supplements-were determined through a medication review completed during each visit encounter. During the retrospective EHR review, a vitamin D supplement was documented on the day of the vitamin D screening, then it was recorded as such. However, the actual dose of over the counter vitamin D supplements remains subjective.

Chapter 2

Review of Literature

Introduction

Vitamin D has generated considerable interest in the medical literature over the last decade. However, there remain inconsistencies between experts on a shared definition of hypovitaminosis D, what constitutes an optimal level of circulating 25(OH) D, and the daily dietary intake level which is considered sufficient (Holick, 2007). Nonetheless, mounting evidence continues to support a link between low levels of serum 25(OH) D and a variety of both skeletal and non-skeletal disorders that can occur over the life span (Huh & Gordon, 2008). Due to these linking factors, children and adolescents with SCD may be particularly vulnerable to the effects of hypovitaminosis D.

Prevalence studies conducted at pediatric medical institutions in the northeastern U.S. have found the SCD population may be more susceptible to hypovitaminosis D compared to matched control subjects or non SCD patients (Buison et al., 2004; Rovner et al., 2008). Compounded by inherent risk factors associated with biological characteristics, environmental influences, and co-morbidities, these patients can have potential serious health consequences due to low levels of vitamin D. Therefore, early identification, prevention and treatment of hypovitaminosis D may have significant, positive health outcomes. This information will enable the nurse practitioner to develop a well-designed prevention and treatment program to promote healthier quality outcomes.

Critique and synthesis of Empirical literature

Vitamin D classification by 25(OH) D level.

Much disagreement and many inconsistencies across the literature have been found over what serum markers differentiate between vitamin D deficiency and insufficiency. However,

most health officials now agree that a 25(OH) vitamin D level ≤ 20 ng/mL constitutes a diagnosis of vitamin D deficiency. Concentrations ≤ 10 ng/mL are considered severely deficient, and vitamin D levels 21-29 ng/mL indicates an insufficient amount of circulating vitamin D (Holick & Chen, 2008). Moreover, current recommendations from adult and pediatric health officials endorse conflicting amounts of daily requirements of vitamin D and do not provide any different recommendations for those that live in less sunny locations or higher latitudes, who may benefit from ingesting higher amounts of vitamin D (Holick & Chen, 2008). However, most experts agree that the only way to detect a person's vitamin D status is to measure the major circulating volume of 25(OH) D (Holick, 2004).

Prevalence and significance of hypovitaminosis D.

Hypovitaminosis is considered pandemic (Holick & Chen, 2008). Despite significant overall medical advances within this century, about one billion individuals globally are affected by hypovitaminosis D (Naeem, 2010). Overall, the prevalence rate of people in the U. S. with hypovitaminosis D is 41.6% (Forrest & Stuhldreher, 2011). This finding is much higher in minorities, with 82% of African Americans and 69% of Hispanics having vitamin D levels low enough to be considered vitamin D deficient (Forrest & Stuhldreher, 2011).

Hypovitaminosis D has been reported at high rates among children (Huh & Gordon, 2008; Rajakumar, Fernstrom, Janosky & Greenspan, 2005; Sullivan, Rosen, Halteman, Chen, & Holick, 2005), and teenagers in several clinic sites in the U.S. (Gordon, DePeter, Feldman, Grace, & Emans, 2004; Looker, Dawson-Hughes, Calvo, Gunter, & Sahyoun, 2002).

Accumulating evidence suggest an association between hypovitaminosis D with an increased risk of developing a chronic illness (Holick, 2004). While the consequences of extreme vitamin D deficiency may lead to rickets it can also inhibit attaining full height velocity

and bone mass among children (Holick, 2004). Hypovitaminosis D has also been linked to bone and muscle discomfort (Plotnikoff & Quigley, 2003) and reactive airway disease or recurring pulmonary symptoms in children (Camargo et al., 2011). Additionally, children who received vitamin D supplementation from the age of 1 had an 80% decrease in risk of developing Type I diabetes (Hypponen, Laara, Reunanen, Jarvelin, & Virtanen, 2001). Moreover, an increased intake of vitamin D has been suggested to decrease the risk of acquiring rheumatoid arthritis (Merlino, Curtis, Mikuls, Cerhan, Criswell, & Saag, 2004), claimed to be an effective treatment for hypertension (Krause, Buhring, Hopfenmuller, Holick, & Sharma, 1998), and may reduce the risk of colon cancer (Garland et al., 1985 as cited in Holick, 2004). Although all of these risk factors associated with hypovitaminosis D are noteworthy, pulmonary complications and bone and muscle pain maybe important variables to study in the setting of pediatric SCD, as both of these issues are related to significant morbidity and mortality.

Seasonal influences are known to be a major contributor to the fluctuations in circulating vitamin D levels; higher serum concentrations of 25-hydroxyvitamin D [25(OH) D] are prominent in the warmer months and lower levels of circulating 25-hydroxyvitamin D occur during the winter months (Holick & Chen, 2008). Any barrier that prevents the transmission of UVB rays to earth's troposphere, or diminishes UVB exposure to the skin will affect absorption of vitamin D3 synthesis (Holick & Chen, 2008). Therefore, other risk factors of hypovitaminosis D that may be important to children and adolescents with SCD living in southwestern PA include, darker skin pigmentation, higher latitude and decreased outdoor activities (Holick, 2004; Naeem, 2010). And despite improvements in air quality, some metropolitan regions in southwestern PA continue to have some of the worst air pollution in the U.S. (Clean Air Task Force, 2011).

Prevalence of hypovitaminosis D in northeastern U.S.

Rajakumar et al., (2005) examined a convenience sample of 41 black children between the ages of six to ten years living in the vicinity of Pittsburgh, Pa (latitude, 40° north). Children were enrolled during winter months and early spring in which 49% (n = 20) were found to have vitamin D insufficiency (≤ 20 ng/ mL). The cohort received 400 international units (IU's) of supplemental vitamin D3 daily for one month. After treatment with vitamin D, 18% of the participants continued to have insufficient levels of vitamin D. Although these findings show that an impressive 82% reached sufficient levels of vitamin D, the researcher determined the 18% who did not achieve sufficiency may have been attributed to the short duration of treatment or possibly due to inadequate doses of vitamin D.

Gordon et al., (2004) studied 307 subjects, ages 11 to 18 years in a primary care setting from Children's Hospital in Boston (latitude, 42° north). Participants were enrolled in an observational study during their annual well child physical examinations. Twenty-four percent (n = 74) were found to be vitamin D deficient (≤ 15 ng/mL), among this cohort, five percent (n = 14) were determined to be severely deficient (≤ 8 ng/mL). Additionally, forty-two percent (n = 129) were vitamin D insufficient (< 20 ng/mL). Using a multivariate model, race, physical activity, BMI, season and milk and juice consumption were independent predictors of low levels of vitamin D.

Weng, Shults, Leonard, Stallings, & Zemel (2007) investigated 382 healthy African American and white children and teenagers ages 6-21 years from Philadelphia, PA (latitude 40°). Among participants enrolled during the winter months, the overall prevalence rate of hypovitaminosis D (< 30 ng/mL) was 68%. Among the African American cohort, the prevalence of hypovitaminosis D was 94% whereas the prevalence among white participants was 51%. The

researchers concluded that black race, older age, winter season and total daily vitamin D intake were significantly associated with lower vitamin D levels. However, the study findings did not find a significant correlation between fat and lean mass and vitamin D levels.

Hypovitaminosis D in pediatric sickle cell disease.

Rovner et al., (2008) sought to compare vitamin D levels among children with SCD (Hgb SS) and healthy African American controls living in the same locale of Philadelphia, PA (latitude 39.95° N). Results showed that median vitamin D levels were 15 ng/mL among children with Hgb SS and 21 ng/mL among their healthy African American counterparts. Vitamin D deficiency was determined to occur in 33% of the cohort with Hgb SS (< 11 mg/mL), and in 9% of the healthy participants. Ninety-three percent of the children with Hgb SS and 90% of healthy subjects had vitamin D insufficiency (< 30 mg/mL). Rovner et al., (2008) concluded that the risk of VDD was five times greater among participants with SCD than was found in their healthy counterparts.

Buison et al. (2004) examined vitamin D levels among African American children and adolescents with Hgb SS type SCD. Vitamin D levels were obtained from 65 participants, ages 5-18 years of age, recruited from the Sickle Cell Center at Children's Hospital of Philadelphia. The mean serum vitamin D concentration for children with suboptimal vitamin D was 18.4 $\pm$ 5.9 nmol/L compared with 38.6 $\pm$ 11.4 nmol/L in subjects with sufficient vitamin D levels. Hgb SS subjects with decreased vitamin D biomarkers were older, with a marked seasonal effect with vitamin D levels dropping precipitously from summer to spring (31.4 nmol/L to 17.95 nmol/L) and they consumed less vitamin D and calcium dietary sources. The researchers did not find any differences for among gender or BMI.

The studies reviewed were conducted utilizing observational vitamin D prevalence rates in the United States among convenient samples of children and adolescents at their respective hospital centers. Therefore, prevalence rates differed depending on the number of participants and region. There were no consistent parameters for vitamin D deficiency, insufficiency or sufficiency. There was also no consistent use of serum concentrations, as some studies reported results in nanograms per milliliter while others reported vitamin D values in nanomoles per liter. Due to the variability in the age ranges utilized in each study, it was difficult to ascertain which age groups were at higher risk of vitamin D deficiency with any consistency. Risk factors for vitamin D deficiency that were consistent included season, older age, and darker pigmentation. Despite these limitations, the results do suggest that healthy children and adolescents and those with SCD can be affected by low levels of vitamin D.

The majority of studies examining vitamin D deficiency in sickle cell have only included patients with Hgb SS disease. However, to this researcher's knowledge, studies that have included other sickle cell genotypes in vitamin D screening had too few non Hgb SS subjects, and therefore did not compare vitamin D biomarkers between patients with sickle-hemoglobin C disease (Hgb SC), sickle beta-plus-thalassemia (HgbS/β^{+}), or sickle beta-zero-thalassemia (HgbS/β^{0}).

Biological correlates of vitamin D

Vitamin D and age, gender and BMI

Multifactorial variables have been found to play a role in low levels of vitamin D, and age, gender and BMI have been considered as potential determinants. Age may play a factor in vitamin D deficiency because as individuals grow older less vitamin D is produced cutaneously and decreased amounts of vitamin D are absorbed through the diet. Females may have decreased

circulating vitamin D levels because they have more adipose tissue than males, in addition to unique social factors such as spending less time outdoors and wearing more sunscreen (Johns Hopkins Medicine, n.d.). Although these two variables have been inconsistently reported as independent predictors of vitamin D deficiency, some studies have suggested female gender (Bentli et al., 2013) and an older age may be risk factors (Stein et al., 2006; Willis, Laing, Hall, Hausman, & Lewis, 2007). Despite these inconsistencies these correlates remain a focus of interest from a biological and demographic standpoint.

A low BMI in the setting of SCD could be another potential causative factor. Although not fully understood, poor growth and nutritional status and delayed puberty are common findings in children with SCD (Barden, Kawchak, Ohene-Frempong, Stallings, & Zemel, 2002). Vitamin D_3 is a lipid soluble vitamin which is produced through UVB exposure and can be deposited in body fat to be used when stores are depleted during the winter months when there is less abundant sunshine (Holick, 2004). Barden et al. (2002) found that some children with SCD have lower z-scores for upper arm fat mass, decreased fat free mass, muscle wasting and inadequate protein stores in comparison to their control group. Therefore, children and adolescents with SCD who are underweight may be at a two-fold risk for VDD given their darker pigmentation, in addition to depleted fat reservoirs in which to store any excess vitamin D. Children with the SS or the $S\beta^0$ genotypes typically have more severe disease courses and are at higher risk for nutritional deficiencies due in part to poor dietary intake and increased energy expenditure (Rovner et al., 2008).

Conversely, it has been shown in mouse models that vitamin D can accumulate in adipose tissue that causes the release of 25(OH) D from these reservoirs to be very slow which results in deficiency of 25-hydroxyvitamin D (as cited by Lagunova, Porojnicu, Lindberg,

Hexeberg, & Moan, 2009). In other studies among youth, vitamin D deficiency has been associated with greater fat mass and increased BMI (Gordon et al., 2004; Weng et al., 2007).

Vitamin D and Skin Type.

Any barrier that prevents the transmission of UVB rays to earth's troposphere, or diminishes UVB exposure to the skin will affect absorption of vitamin D_3 synthesis (Holick & Chen, 2008). Persons with increased melanin and darker skin pigmentation, those with aging skin, those who regularly apply sunblock, individuals who mostly work indoors, and those who wear excessive clothing are all at risk of vitamin D deficiency (Holick, 2004; Naeem, 2010). Additionally, those persons with darker skin tones need extended exposure to sunlight to produce similar concentrations of vitamin D, as compared to fair-skinned people (Holick, 2004).

Vitamin D and nutrition.

Sometime in the early 1930s, the U.S. government began providing recommendations to parents about the advantages of sun exposure in an effort to combat vitamin D deficiency rickets (Holick & Chen, 2008). Concomitantly, milk was fortified with 100 IU's of vitamin D2 per eight ounce serving and was seemingly successful in eradicating rickets in the U.S. and Europe (Holick & Chen, 2008). Vitamin D is often referred to as the "sunshine vitamin" because approximately fifty to ninety percent of vitamin D synthesis occurs when the skin is exposed to UVB rays produced by the sun. Although the remainder of vitamin D is most often from dietary sources, most natural foods contain little of this important vitamin (Naeem, 2010).

Results of the 2005-2006 National Health and Nutrition Examination Surveys suggest that children and adolescents are not consuming enough vitamin D to meet their daily requirements (Linus Pauling Institute, 2012-2015). Naturally occurring vitamin D is limited among food sources and food items fortified with vitamin D may be insufficient (Holick, 2004).

Natural human foods that contain varying amounts of vitamin D include items like oily fish, such as mackerel, salmon, herring, or supplements such as cod liver oil. Interestingly, it has been found that farm raised fish have considerably less vitamin D than those fish caught in the wild, which may be attributable to the inherent vitamin D occurring in the food chain, but depleted in pellet fish food (Holick & Chen, 2008).

In the U.S. today, milk, some juices, breakfast cereals, breads, yogurts, margarines, and cheeses are fortified with vitamin D (Holden, et al., 2008; Holick & Chen, 2008). Infant formula in the U. S. and Canada is mandated to be fortified with vitamin D (NIH, 2011). Approximately 60% of dietary supplemental vitamin D comes from fortified food sources, however, those individuals at greater risk are consuming these products in lesser amounts (Calvo & Whiting, 2013). There are currently unique practices of "bio addition" being implemented so that more vitamin D can be added in foods such as exposing post-harvested mushrooms to ultraviolet light or fortifying animal feed with vitamin D (Calvo & Whiting, 2013). Although a novel approach, the production costs of bio addition could potentially drive up these food prices, making it less affordable for those who would otherwise benefit.

Environmental correlates of vitamin D.

Season, along with latitude and time of day can affect vitamin D synthesis. During the winter months, UVB rays enter the earth's atmosphere at a more oblique angle allowing the ozone layer to absorb them more rapidly causing a decrease in D3 production (Holick, 2004). In the U. S., more than fifty percent of African Americans are estimated to be either chronically or seasonally affected by vitamin D deficiency (Holick, 2004). Researchers found in the third National Health and Nutrition Examination Survey that 42% of African American females aged 15-49 years were vitamin D deficient at the end of the winter season (Nesby-O'Dell et al as cited in Holick, 2004). Similarly, 32% of students and physicians at Boston Medical Center were

noted to have insufficient levels of circulating vitamin D at winter's end (Tangpricha, Pearce, Chen, & Holick, 2002, as cited in Holick, 2004).

Other environmental factors that have been explored include cloud cover or low or high altitude (Melamed & Kumar, 2010). On average, southeastern PA has about 59 sunny days and 103 partly sunny days which includes a cloud covering of 40-70% during the daytime (Current Results, 2015). An estimated 70% of fine particulate matter can be measured in southwestern PA resulting from upwind emissions from power plants beyond their boundaries as the area continues to face challenges in meeting ozone standards (Fraser, 2013). This increased amount of fine particulate matter may create a barrier for ultraviolet B rays to reach the earth, thus preventing cutaneous formation of vitamin D3.

Co-morbidities.

The literature cited a well-known link between hypovitaminosis D bone pain and muscle discomfort associated with osteomalacia in children and adults (Holick, 2004; Straube, Moore, Derry, & McQuay, 2008). However, what remains not fully understood, is the connection between inflammatory diseases and the presence of inadequate levels of Vitamin D which, in vitro, has been shown to inhibit the inflammatory response (Zhang et al., 2012). There has been heightened interest in the overlap of the symptoms of pain and low levels of vitamin D, as evidenced by the mounting literature exploring these two correlates. Although some studies have shown an association between chronic pain and deficient levels of vitamin D, there remains no clear evidence to implicate vitamin D deficiency in the pain experienced in SCD (Osunkwo et al., 2011; Straube et al., 2008). Further investigation of these two symptoms is therefore required to better understand their association, if any.

Jackson et al. (2012) conducted a study to assess for co-morbidities associated with Vitamin D deficiency in SCD. Vitamin D levels were measured in 139 children aged approximately 8 to 15 years. Among the participants, 96.4% were considered to have vitamin D deficiency (≤ 20 ng/mL). Of these, a severe vitamin D deficiency ≤ 10 ng/mL was present in 64.0% of the participants and only 2.2% of the cohort were found to have sufficient levels of vitamin D (> 30 ng/mL). Levels of vitamin D were inversely related to increasing age. Additionally, there was an association between vitamin D and pulmonary function with severe vitamin D deficiency (≤ 10 mg/mL) being a predictor for a lower forced expiratory volume (FEV1). Therefore vitamin D levels were associated with pulmonary dysfunction but there was no association with either rates of acute pain or acute chest syndrome episodes.

Among the general population, asthma is the most frequently occurring chronic illness in childhood (Nordness, Lynn, Zacharisen, Scott, & Kelly, 2005). Asthma disproportionately affects African Americans and occurs in approximately twenty percent of children (Field & DeBaun, 2009; Khoury, Musallam, Mroueh, & Abboud, 2011; Nordness et al., 2005). Hypovitaminosis D also disproportionately affects African Americans (Forrest & Stuhldreher, 2011) which could be linked to a more complex asthma course (Khoury et al., 2011), and because the prevalence of asthma in SCD is estimated to be between 30-70%, (Morris, 2009), this makes asthma one of the most common comorbidities among individuals with this hemoglobinopathy (Field & DeBaun, 2009).

Among the general population, exacerbations of asthma triggered by respiratory tract infections are the leading cause of morbidity, in addition to being a major contributor to multiple days of work missed as well as school absences (Brehm et al., 2010). Vitamin D is a hormone with steroid like properties and is thought to play a role in modulating the immune system in

decreasing asthma severity along with a variety of other complex health conditions (Naeem, 2010). What is more, asthma complications have been found to account for the majority of healthcare costs in the U. S., and therefore, Hypovitaminosis D could be linked to the severity of pulmonary dysfunction among patients living with this condition (Brehm et al., 2010). Finally, low levels of vitamin D among children and adults have been correlated with impaired lung function (Sutherland, Goleva, Jackson, Steven, & Leung, 2010; Wu et al., 2012).

Therefore the African American population is not only at higher risk of having vitamin D deficiency, but also SCD and asthma occurring simultaneously (Nordness et al., 2005). For individuals with SCD, the lung is a prime target organ for acute and chronic complications to occur, and is the second most common cause of hospitalizations among this cohort (Hostyn et al., 2013). Pulmonary complications also carry a high risk for morbidity and mortality in persons with SCD (Knight-Madden et al., 2005).

Medications and vitamin D.

Inhaled corticosteroids.

Sutherland et al. (2010), examined the effect of vitamin D and inhaled corticosteroids among adult asthma patients and found that decreased vitamin D levels were connected with poorer lung function, and a reduced response to inhaled corticosteroids. The researchers recommended that vitamin D supplementation may improve the severity of asthma symptoms and improve treatment response. Similarly, Wu et al. (2012) compared children with VDD, VDI, and asthma who were treated with inhaled corticosteroids. After one year of treatment, those children who were VDD showed less improvement in lung volumes than those children who had sufficient amounts of circulating vitamin D. The researchers concluded that decreased circulating 25(OH) D levels may be associated with a hyper responsive airway, impaired

pulmonary function and decreased response to inhaled corticosteroids. Therefore vitamin D supplementation in patients with asthma may improve the asthma symptoms and response to inhaled corticosteroid treatment. Although studies examining these two correlates have found conflicting results, vitamin D supplementation as an adjunct to improve clinical efficacy of inhaled corticosteroids continues to be explored in the literature.

Vitamin D supplements.

The Food and Nutrition Board (FNB) at the Institutes of Medicine developed intake reference values for vitamin D and other essential nutrients (NIH, 2011). A recommended daily allowance of vitamin D was established by the FNB that has been deemed adequate to promote skeletal health and calcium absorption among healthy individuals (NIH, 2011). These FNB guidelines recommend a daily dietary intake of 400 IU per day for infants up to age one and 600 IU per day for children. The guidelines were created for those who are healthy, which seemingly leaves the application to children with chronic illnesses somewhat ill-defined (Abrams, Coss-Bu, & Tiosano, 2013).

Vitamin D Prevention and Screening Guidelines.

More attention is warranted to further assess the connection between vitamin D and the potential impact that it has on children with SCD so that appropriate prevention intervention strategies can be initiated (Jackson et al., 2012). However, at present, the standard of practice for identifying vitamin D clinical risk factors, and corresponding screening and treatment recommendations are inconsistent in the literature. In 2011, The Institute of Medicine (IOM) Sub-committee on dietary intake for vitamin D and calcium concluded that recommendations for screening practices were beyond the scope of their assignment, and these guidelines might be better addressed by federal bureaus or professional associations. The Sub-committee finalized

their report by advising that a serum 25(OH) D level of 16 ng/mL would cover the requirements for about 50% of the population and 20 ng/mL would meet the requirement for up to 97.5% of the population (Ross et al., 2011). However, the U.S. Endocrine Society (Holick et al., 2011) does not agree with the IOM's recommended cut off level of 25(OH) D at 20 ng/mL and maintains that an appropriate vitamin D level should be at least 30 ng/mL. It was also suggested that a new national vitamin D prevalence study may be warranted to better support the IOM's recommendations (Holick et al., 2011).

In a 2010 report by the IOM, the recommended daily allowance of vitamin D was increased from 400 IU to 600 IU for children over the age of one; however, among this cohort only 1 in 3 was taking vitamin D (Staple & Teach, 2011). Given this, it may seem negligent to not advise a combined vitamin D nutrition and sensible sunshine prescription recommendation as part of a prevention intervention and treatment regimen to combat hypovitaminosis D. In this way, illnesses and hospitalizations may be reduced and cost effectiveness and quality of life increased.

According to U.S. Endocrine Society's Clinical Practice Guidelines (CPG) that were published in the Journal of Clinical Endocrinology and Metabolism (Holick et al., 2011), the latest recommendations on prevention and treatment of hypovitaminosis D were featured. This CPG also included screening recommendations for populations identified as at risk for this condition which included African American and Hispanic children, adolescents and adults. Other subjects at risk in which 25(OH) D screening was indicated were those with: (a) Skeletal problems, (b) Kidney and hepatic impairment, (c) Malabsorption syndromes, (d) Hyperparathyroidism, (e) Using certain medications such as steroids, antiseizure, and antifungals, (f) Pregnant and lactating women, (g) Breast-fed infants, (h) Elderly persons with a

history of falling or idiopathic fractures, (i) Obese children, (j) Granuloma forming disorders, (k) Some lymphomas, and (l) Maternal vitamin D deficiency. Kennel, Drake, and Hurley (2010) identified other individuals who may be at clinical risk for hypovitaminosis D, such as those with overall decreased intake through oral means, malnutrition or lack of adequate sun exposure. Additional influences also included were persons living in more northern latitudes, sun avoidance preferences, cultural dress practices, and sunscreen application habits and season, which can also limit the production of vitamin D (Kennel et al., 2010).

The sickle cell subjects who attend the non-profit tertiary children's hospital in southwestern PA included in the current project are primarily African American, who live in a northern latitude city (40.44° N) which has only about 59 sunny days per year. This, coupled with the research findings that low levels of circulating 25(OH) D is increased among SCD participants compared to their healthy counterparts was merit enough to consider this cohort at risk for hypovitaminosis D. Based on the recommendations by the CPG, vitamin D screening among SCD patients was added to our Health Prevention and Maintenance guidelines as a standard of care in April of 2014.

Rationale for the study

While there is growing corroboration of the link between a variety of health conditions and hypovitaminosis D, the effects of vitamin D on children and adolescents with SCD remains limited. Due to this gap, this current project's aim was to investigate the prevalence of hypovitaminosis D and its impact on the biological, environmental and medication correlates among patients enrolled at a non-profit tertiary children's hospital in southwestern PA with SCD.

The literature review contained mounting evidence of increasing concern for low levels of vitamin D worldwide, the associated risk factors, and the nutritional initiatives to remedy this problem. There is also an increasing interest in the potential adjunct modalities that early

screening, prevention, nutritional support, education, and treatment can lend. This accumulating body of literature, has as its aim, to investigate these alternatives as a means to diminish disease comorbidities in hopes of preventing further disabling symptoms and improving quality of life. Because individuals living with SCD may be at an even higher risk of being vitamin D deficient than their healthy counterparts, this study sought to explore the potential relationship between hypovitaminosis D and the identified variables.

Lastly, nurse practitioners need to be keenly aware of populations at risk for vitamin D deficiency to be able to provide education, implement screening, treatment, and nutritional counseling and strategies in an effort to prevent potential health consequences, and thereby contribute to improved patient health outcomes. Thus, deficiency in vitamin D among patients with SCD may represent a treatable etiology and therefore standards of care should be carefully considered.

Chapter 3

Methods

Design

A retrospective, descriptive, cross-sectional correlational design was used to gather quantitative data to ascertain the prevalence of hypovitaminosis D among children and adolescents with SCD who attend a pediatric tertiary hospital in southwestern PA. The subjects' vitamin D levels were then correlated with the independent variables (biological and environmental factors and vitamin D supplements) to identify any associations with hypovitaminosis D. The subjects' vitamin D levels were also correlated with the dependent variables (comorbidities and inhaled corticosteroid strength) to identify whether low levels of vitamin D were associated with more hospitalizations for comorbid conditions and to investigate if lower levels of vitamin D were linked to higher strength asthma inhalers. The vitamin D

screening process began in April of 2014 and continued through January 2015 to include all four seasons. A retrospective EHR review was employed to assess vitamin D levels among this single institution cohort to determine the prevalence and to compare these biomarkers to the variables aforementioned, in order to evaluate for any associations.

Population

The population included a convenience sampling of 104 children and adolescents ages 1-20 years with SCD who attended a nonprofit children's hospital in southwestern Pa. The use of a convenience sample from the children's hospital and clinics assisted with maximizing the number of patients screened for vitamin D during their routine visit. Patients who met the following inclusion criteria were included in this project:

1. Patients 1-23 years old diagnosed with SCD
2. Followed at the non-profit children's hospital in southwestern PA; and
3. Scheduled for routine blood analysis during their clinic visit as part of their clinical care.

Procedures

The UPMC Quality Improvement Committee approved this as a quality improvement project to examine the association of vitamin D levels on the variables of interest and perform a retrospective EHR review. Additionally, this project was endorsed by the Carlow University Internal Review Board (IRB) as a quality improvement project which does not meet the federal definition of research according to 45 CFR 46.102(d) and therefore does not necessitate IRB oversight.

All subjects were patients followed by the pediatric hematology clinic with a diagnosis of SCD, who met eligibility criteria for vitamin D screening, were identified by the researcher through the course of clinical care. A review of the patient's EHR by the researcher is standard

practice in order to examine any updated health information data which includes demographic information, clinic and hospitalization records, medical/surgical history, past and recent laboratory results, and medication list. The patient's EHRs were also reviewed by the researcher to confirm the accuracy of sickle cell status and genotype.

Subjects underwent a blood analysis for hypovitaminosis D during a routine clinic visit. The 25-hydroxyvitamin D assay is considered to be the best evaluative measurement of vitamin D status (Zerwekh, 2008). At the project site's laboratory, this assay includes Vitamin D, 25-OH, Total; Vitamin D, 25-OH, D_3; and Vitamin D, 25-OH, D_2. Specimens were processed through a chemistry technique called Liquid Chromatography/Mass Spectrometry (LC-MS). While it is preferred that patients are fasting, it is not required. The blood was collected in the amount of 0.5mL into a red top Serum Separator Tube (SST®) and transported to the chemistry laboratory for processing at room temperature. Testing for vitamin D deficiency has been an established standard of care for this population, and therefore the 25(OH) D blood analysis was covered by each patient's insurance carrier. The project was designed to minimize all possible and undue harm to subjects, and therefore all blood draws for the purposes of vitamin D assessment coincided with the patient's routine clinic appointment and scheduled laboratory studies.

Data was obtained through a retrospective EHR review and then populated into the Vitamin D Correlates Tool. The information collected was completed by the researcher that included the following:

1. **Biological data collected**-included the subject's age, gender, sickle cell genotype, BMI, skin type classification, and milk preference on the day the vitamin D level was drawn. The subject's height and weight were obtained as a routine part of their clinic visit,

whereby their body mass index was calculated according to the CDC (n.d.) for pediatrics ages 2-20, and adults ages 21 and above. The skin type was visually assessed by the researcher during the subject's clinic visit under a combination of fluorescent and natural light. Skin color was evaluated from the dorsum of the subject's hands and face. A skin classification was assigned based on Fitzpatrick's Scale (Fitzpatrick, 1996) and HTetronics (2011) visual chart by using Fitzpatrick's skin classification scale (I-VI). The guardian or subject was also asked about milk preferences as a part of the patient's dietary review. Milk preferences were categorized by "yes", "no" or "sometimes", to the patient's response to the question "Do you like milk?"

2. **Environmental factors**-were validated during the time the participant's vitamin D level was drawn. The population density of each zip code was then obtained by using the Home Town Locator® website (2015). The season in which the vitamin D analysis occurred corresponded to the start date of each new season: spring 3/20/14, summer 6/21/14, fall 9/22/14 and winter 12/21/14.
3. **Medications**-as documented in the subject's EHR were reviewed retrospectively to determine if the subject was taking or prescribed vitamin D supplements. Corticosteroid inhaler dose was also retrospectively verified for subjects with a known diagnosis of asthma at the time of the 25(OH) D analysis.
4. **Hospitalizations**-were retrospectively reviewed for pain episodes and ACS from the date that the subject's vitamin D level was drawn to 5 years prior. To substantiate an ACS diagnosis, radiologist's impressions were reviewed for each ACS admission to confirm new pulmonary changes. If no new findings were documented, a diagnosis of ACS was dismissed. To endorse a VOC hospital admission, it was verified that the participant

received intravenous opioid pain management. If no opioids were administered during the admission, then the VOC hospitalization was not counted.

Instruments

Fitzpatrick Skin Type Scale.

The Fitzpatrick Skin Type Scale (Fitzpatrick, 1988) categorizes skin color based on their tolerance to sunlight (Appendix C1). Although subjective by the user, the Fitzpatrick Scale is a noninvasive and simple tool that is widely used in the dermatology field for evaluation of skin pigmentation (Sachdeva, 2009). Skin types are classified as the following: Type I skin color is pale white, Type II are fair skinned, Type III have light to medium skin color, Type IV have golden to olive skin tones, Type V skin color is bronze to brown, and Type VI complexions range from deep mahogany to ebony.

HTetronics Skin Tone Visual Chart.

A skin color chart is also a simple, convenient and noninvasive tool that can be used to evaluate skin tone. A skin tone visual chart adapted from Fitzpatrick's skin groupings devised by HTetronics (2011) was utilized to provide more consistency in determining the patient's skin classification (Appendix C2).

Vitamin D Correlates Tool.

The Vitamin D Correlates Tool (Appendix D) was a researcher-developed instrument that listed 12 factors that have been identified in vitamin D studies, such as the following: biological factors (i.e., age, gender, genotype, BMI, skin type, and milk preference), environmental factors (season, and population density), co-morbidities (i.e., ACS and VOC crisis admissions), and medications (i.e., inhaled corticosteroid strength and vitamin D supplements).

The Vitamin D Correlates Tool was developed based on the investigator's knowledge and experience in caring for children and adolescents with SCD, in collaboration with expert opinion from pediatric hematology clinicians, and from the literature review. Prior to use in this project, the tool was reviewed by a team of experts consisting of a pediatric hematologist, a Sickle Cell Nurse Case Manager, and a Sickle Cell Nurse Practitioner and was revised based on their feedback as needed. The biological factors, environmental factors, co-morbid related hospitalizations, and medications were recorded on the Vitamin D Correlates Tool during a retrospective electronic chart review from spring of 2014 through winter 2015.

Home Town Locator® (2015).

This website was utilized to determine the population density in which each subject resided. Participants' zip codes were entered into the "find cities by zip code" prompt which led to the corresponding city profile. Within each city profile contained population data and demographics including population density defined as total population per square mile.

Data analysis plan

Quality control.

Data were collected and entered into the Vitamin D Correlates Tool that was maintained on an encrypted password protected computer and secured hospital network. As subjects were screened for inclusion and agreed to participate in the project, they were assigned a number and a hard copy of the data forms were maintained by the researcher and kept in a locked file cabinet. Participant identifiers were not recorded in the EHR or any other record database.

Statistical analysis.

Statistical analysis of the vitamin D quality improvement project utilized a retrospective, descriptive cross-sectional correlational method. A cross-sectional approach was used to

examine the overall prevalence of hypovitaminosis D with a breakdown into the classifications of circulating 25(OH) D including: severe vitamin D deficiency, vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency. This made it possible to identify any associations among the independent and dependent variables of interest from a certain point of time. Quantitative descriptive statistics were employed to analyze and describe the data retrieved from the date the vitamin D screening took place in relation to a retrospective EHR review to ascertain the season, patient's residence for zip code, age, gender, sickle cell genotype, hospital admissions over the last five years, medication list, BMI, milk preference and skin color by using Fitzpatrick's Skin typing scale.

The Wald test was utilized to test the significance between the biological, environmental and vitamin D supplements in predicting lower levels of vitamin D. The test was also employed to examine which factors were associated with co-morbidities and variables associated with inhaled corticosteroids. A logistic regression model was created to log the odds of having hypovitaminosis D and to describe whether each of the variables were significant in predicting total vitamin D, vitamin D sufficiency (> 30 ng/mL), vitamin insufficiency (21 ng/mL - 29 ng/mL), vitamin D deficiency (11 ng/mL - 19 ng/mL) and severe vitamin D deficiency (< 10 ng/mL). Factors that influence the odds of having more severe hypovitaminosis D were modeled using an ordinal logistic regression. This approach also allowed for inferences to be made about possible associations between the varying classifications of vitamin D biomarkers and other characteristics being investigated. Chi-square tests evaluated whether there was a within-group difference.

All of the data were analyzed using the SAS version 9.3® (2012) statistical package software. The statistical analysis began descriptively to investigate the data for completeness.

Frequency distributions were presented on tables to exhibit the vitamin D level with the corresponding variables of interest. Additionally, summary statistics such as odds ratio, 95% confidence intervals, standard deviations and means were used to examine the probability of significance between the variables ($p < 0.05$).

Statistical analysis reported in the following Results section included correlations between findings and the current project's Research Questions (RQ).

RQ 1: What is the prevalence of hypovitaminosis D?

RQ2: What are the factors associated with hypovitaminosis D?

RQ3: Is there a relationship between the factors that influence hypovitaminosis D?

RQ4: Is there a relationship between hypovitaminosis D that influence co-morbidities?

Chapter 4

Results

This chapter offers the results of the completed project. It includes sections on the sample population's prevalence of hypovitaminosis D, and the biological, environmental, co-morbidities, and medication responses correlates in relation to the vitamin D categories.

Analysis of Data

Sample population.

Through a retrospective EHR review, this Quality Improvement Project used a quantitative, cross-sectional study design to identify the biological, environmental, co-morbidities and medication correlates of hypovitaminosis D among children and adolescents with SCD. Serum 25(OH) D levels were determined for participants ages 1-20 with SCD who were enrolled at a non-profit tertiary children's hospital. According to the sites' Health Maintenance and Prevention Guidelines, 104 patients were screened with a 25-hydroxyvitamin D

panel beginning in mid-April of 2014 and extended through early January of 2015. All of the subjects who underwent vitamin D screening were identified during the course of their clinical care and were scheduled for a routine blood analysis.

Prevalence of hypovitaminosis D.

According to accepted vitamin D classifications (Holick, 2007), 11.5% of project subjects were found to be vitamin D sufficient (≥ 30 ng/mL), 32.7% insufficient (20 - 29 ng/mL), 39.4 % with deficiency (10 - 19 ng/mL) and 16.4% with vitamin D deficiency (< 10 ng/mL). The mean serum vitamin D level for these 104 subjects was 19 ng/mL (SD = 10.1). Among these subjects screened, there was an overall prevalence rate of 88.5% (< 30 ng/mL) who were found to have hypovitaminosis D (Table 1).

Table 1

Prevalence of vitamin D levels according to serum 25(OH) D levels

25(OH) D	n	Prevalence	*M*	*SD*
Severe (<10 ng/mL)	17	16.40%	5.7	1.8
Deficient (11-19 ng/mL	41	39.40%	14.7	3.1
Insufficient (20 - 29 ng/mL)	34	32.70%	23.7	2.7
Sufficient (>30 ng/mL)	12	11.50%	39.3	5.7

Biological Correlates.

Biological characteristics of the sample population included: age, gender, genotype, BMI, skin classification, and milk preference. Age groups were broken down into 4 year increment categories as follows: 1-5 (17.3%), 6-10 (30.8%), 11-15 (24%), and 16-20 (27.9%). The mean age of the subjects was 10.9 ± 5.7. Hypovitaminosis D (< 30 ng/mL) occurred in 13% of the 1-5 year old age group; in 28% of the 6-10 year old age category; in 27% of the 11-15 year olds; and 32% had levels consistent with hypovitaminosis D in the 16-20 year old age group. Among those subjects who were found to have sufficient vitamin D levels (n= 12), 50% were in the 1-5

year old age group and 50% were in the 6-10 year old age category. No subjects in the 11-15 or 16-20 year old age groups were found to have levels consistent with vitamin D sufficiency (> 30 ng/mL). The mean age of severe deficiency was 14.6 $\pm$ 4.5, and the mean age of sufficient levels of vitamin D was 4.1 $\pm$ 3.0.

Forty-nine females (47.1%) and 55 males (52.9%) were included in this project (n = 104). More females than males were found to have severe vitamin D deficiency (n = 17) (52.9% versus 47.1%), and insufficiency (n = 34) (55.9% versus 44.1%). More males than females were found to have vitamin D deficiency (n = 41) (58.5% versus 41.5%). Vitamin D sufficiency occurred in 33.3% of females and 66.7% of males (n = 12). Mean levels of 25(OH) D observed between females and males were 18.25 ng/mL $\pm$ 9.792 and 19.6 ng/mL $\pm$ 10.28, respectively.

Among the genotypes, HgbS/β^0 (n = 3) had a mean vitamin D level of 32 ng/mL $\pm$ 4.189, Hgb SC (n = 34) subjects showed a mean level of vitamin D of 20.57 ng/mL $\pm$ 10.55, subjects with HgbS/β^+ (n = 8) had a mean vitamin D level of 19.75 ng/mL $\pm$ 6.60, and Hgb SS (n = 58) subjects revealed a mean level of 17.08 ng/mL $\pm$ 8.69. One subject with homozygous sickle cell and X*mn*1 polymorphism had a 25(OH) D level of 52 ng/mL and fell under the "other" category. Subjects with Hgb SS accounted for 55.8% of the total population, Hgb SC represented 32.7% and HgbS/β^0, HgbS/β^+, and the one subject with X*mn*1 polymorphism combined accounted for 11.5% of the population.

The 104 subjects were categorized as 14.4 % (n = 15) were underweight, 63.5% were at a healthy weight (n = 66), 11.5% were overweight (n = 12) and 10.6% were obese (n = 11). Subjects who fell within obese percentile (> 95 percentile) had a mean vitamin D level of 20 ng/mL $\pm$ 7.92; those that were in the overweight percentile (85^{th} - 94^{th} percentile) had a mean vitamin D level of 19.8 ng/mL $\pm$ 5.98; those who were healthy weight subjects (5^{th} - 85^{th}

percentile) had a mean level of 18.67 ng/mL ± 9.67; while those who plotted in the underweight range (< 5th percentile) showed a mean vitamin D level of 12.2 ng/mL ± 7.43. No subject with an underweight status was found to have vitamin D levels within the sufficient range.

Among the skin classifications, the majority of subjects (59.6%) were determined to be type VI; 36.6% were classified as a V; 2.9% with type III; and 1% with type II. No subjects were classified with type I. Subjects with skin type VI had a mean vitamin D level of 17.2 g/mL ± 9.31, while subjects with skin types II, III, IV and V combined had a mean level of 21.8 ng/mL ± 10.4.

Of the subjects who drank milk, 14.4% claimed they liked milked and drank it daily, while 81.7% said they drank milk only sometimes. Subjects who answered that they never drank milk were 3.9% of the population. These responses correlated with mean vitamin D levels of 31.63 ng/mL ±7.25 for daily milk drinkers; 16.98 ng/mL ± 8.58 who drank milk sometimes; and 9.33 ng/mL ± 8.98 for subjects who never drank milk. Table 2 describes the biological characteristics of the population with regard to their vitamin D status.

Table 2

Hypovitaminosis D and Biological Correlates

Characteristic	Hypo-vitaminosis D < 30 ng/mL (n = 92)		Sufficient vitamin D > 30ng/mL (n = 12)	
Age range in years				
1-5	12	(13)	6	(50)
6-10	26	(28)	6	(50)
11-15	25	(27)		0
16-20	29	(32)		0
Gender				
Female	45	(49)	4	(33.3)
Male	47	(51)	8	(66.7)
Genotype				
HgbSS	55	(59.8)	3	(25)
HgbSC	27	(29.3)	6	(50)
HgbS/β0/HgbS/β+/Other	10	(10.9)	3	(25)
BMI				
Healthy	56	(60.9)	10	(83.3)
Underweight	15	(16.3)		0
Overweight	11	(12)	1	(8.3)
Obese	10	(10.8)	1	(8.3)
Skin Classification				
Type I		0		0
Type II	1	(1.1)		0
Type III		0		0
Type IV	3	(3.2)	1	(8.3)
Type V	32	(34.8)	5	(41.7)
Type VI	56	(60.9)	6	(50)
Milk Preference				
Yes	8	(8.7)	8	(66.7)
Sometimes	81	(88)	4	(33.3)
No	3	(3.3)		0

Environmental correlates.

The mean season concentrations of 25(OH) D for spring, summer, fall and winter were as follows: 18.5 ng/mL $\pm$ 10.77; 21.97 ng/mL $\pm$ 9.02; 16.91 ng/mL + 9.019; and 14.6 ng/mL $\pm$ 12.94, respectively. The majority of subjects had serum levels of 25(OH) D taken in the summer (n = 35), and the fall (n = 35). Twenty-nine subjects were screened in the spring and 5 subjects in the winter.

Among subjects enrolled at the non-profit tertiary hospital in southwestern PA, 22.1% (n = 23) live in a rural setting, compared to 77.9% (n = 81) who live in an urban cluster. The mean vitamin D level of those living in a population density less than 1,000 people per square mile was 21.63 ng/mL ±13.48 and those subjects living in an urban cluster with greater than 1000 people per square mile had a mean 25 (OH) D level of 18.31 ng/mL ± 9.08.

Comorbidity correlates.

The mean vitamin D levels among subjects admitted for ACS within the last five years (n = 48) was 18.13 ng/mL ± 7.31 compared to the mean 25(OH) D level among subjects hospitalized for VOC crisis (n = 58) which was 16.69 ng/mL ± 8.95. Subjects without any admissions for either co-morbidity (n = 33) had a mean vitamin D level of 21.94 ng/mL ± 11.73. There were more total pain admissions over the last five years versus hospitalizations required for ACS (58 versus 48). The majority of pain admissions occurred among subjects who fell in the vitamin D deficient classification (n = 23) while those hospitalized for ACS predominantly fell in the vitamin D insufficiency category (n = 21).

Medication correlates.

Approximately 34% (n = 35) of the p subjects screened for hypovitaminosis D (n = 104) carry a diagnosis of asthma. Of those, 66% are prescribed a daily corticosteroid inhaler in addition to their rescue inhaler (n = 23). Those subjects prescribed a moderate dose inhaler (n = 9) had a mean vitamin D level of 17.33 ng/mL ± 8.56 compared to those prescribed a low dose inhaler (n = 14) whose mean vitamin D levels was 22 ng/mL ± 8.89.

Among the total sample, 19.2% (n = 20) reported taking a vitamin D supplement with a mean vitamin D level of 25.8 ng/mL ± 13.39, compared to a mean level of 17.4 ng/mL ± 8.34 among patients who did not report taking a supplement (n = 84). Of those subjects with

sufficient levels of vitamin D (n = 12), 58.3% reported using a supplement. Among subjects with insufficiency (n = 34), 20.6% reported using a supplement; 9.8% of those with deficiency (n = 41) claimed to take a supplement; and 11.8% of subjects with severe vitamin D deficiency said they took a vitamin D supplement (n = 17). Table 3 describes the environmental, comorbidity and medication correlates associated with the vitamin D classifications.

Table 3

Environmental, comorbidities and medications correlates of vitamin D levels

Variable	Severe Deficiency (n=17)	Deficiency (n=41)	Insufficient (n=34)	Sufficient (n=12)
Season				
Spring	35.30%	22.00%	32.40%	25%
Summer	0%	41.40%	41.10%	33.4.%
Fall	52.90%	31.70%	26.50%	33.30%
Winter	11.80%	4.90%	0%	8.30%
Residence				
Urban	76.50%	85.40%	76.50%	58.30%
Rural	23.50%	14.60%	23.50%	41.70%
Hospitalizations				
Acute chest	41.20%	46.30%	61.80%	8.35
VOC	76.50%	56.10%	61.80%	16.70%
Medications				
Low ICS	40.00%	9.10%	56.30%	66.70%
Mod ICS	40%	18.20%	12.50%	33.30%
Vitamin D supplements				
Yes	11.80%	9.80%	20.60%	58.30%
No	88.20%	90.20%	79.40%	41.70%

Intercorrelations of vitamin D and variables.

To provide an underpinning for interpretation, further data analysis was conducted on the variables of interest; biological and environmental factors, hospitalizations related to comorbid conditions (ACS and pain crisis), and medications (vitamin D supplements and inhaled corticosteroids). An ordinal logistic regression was used to evaluate factors related to more severe vitamin D deficiency. Variables were removed from the full model by using a step down

selection method. Age and gender were identified a priori as factors to remain within the final model as these variables have been shown to be correlated in other similar studies.

The multivariate analysis revealed statistically significant biological predictors of lower levels of vitamin D which included: genotype (p = 0.0105), age (p = < 0.0001), BMI (p = 0.0352), and milk preference (p = 0.0001). A statistically significant environmental predictor included: season (p = 0.0035), and, statistically significant medication predictor included taking vitamin D supplements (p = < 0.0001). Variables that were not found to be statistically significant included: gender (p = 0.3533), skin classification (p = 0.8105), urban versus rural residence (p = 0.7403), or asthma (p = 0.9039). Table 4 lists the chi square results for the first iteration of the variable selection model.

Table 4.

Biological, environmental and medication predictor variables of hypovitaminosis D

Variable	DF	Chi-square	*p*
Age	3	23.16	< 0.0001
Gender	1	0.86	0.3533
Genotype	2	9.11	0.0105
BMI	3	8.59	0.0352
Skin type	1	0.06	0.8105
Milk preference	2	17.68	0.0001
Asthma	1	0.01	0.9039
Season	3	13.63	0.0035
Residence (urban vs rural)	1	0.11	0.7403
Vitamin D supplements	1	17.11	< 0.0001

Note: DF = Degrees of frequency

Hospitalizations for comorbid conditions (i.e. VOC crisis or ACS) were determined through a retrospective EHR review. Those subjects requiring intravenous opioids during an admission were identified as having a pain admission. A total of 58 subjects were hospitalized due to VOC over the last five years. A chi-square analysis was performed and revealed no statistically significant relationship between hypovitaminosis D and admissions for pain ($x^2 = 2.57$, df = 3, p = 0.46).

There were a total of 48 subjects who had been admitted for ACS over the last five years. To determine if there was a relationship between factors associated with admissions for ACS, a chi square analysis was performed to determine factors associated with hospitalizations related to ACS. The chi-square analysis showed that there was a weak statistically significant relation between hypovitaminosis D and ACS ($x^2 = 7.83$, df = 3, p = 0.049).

Of the 35 subjects with a diagnosis of asthma, 14 are prescribed low dose inhalers, and 9 are prescribed moderate dosed inhalers. A chi-square test was performed and revealed no statistically significant relationship between hypovitaminosis D and inhaler use ($x^2 = 6.54$, df = 3, p = 0.0882).

Further data analysis was conducted to evaluate the factors that influenced the odds of having more severe hypovitaminosis D which were modeled using an ordinal logistic regression. Chi-square tests evaluated whether there was a within-group difference among these variables of interest. This analysis revealed the following significant results: among the genotypes found to have hypovitaminosis D, subjects with Hgb SS were 3 times more likely than subjects with Hgb SC to have lower vitamin D levels (p = 0.0216); between the age categories, there was an odds ratio (OR = 0.11) of being less likely to have hypovitaminosis D for those ages 6-10 versus those subjects 11-15 years (0.0005); underweight subjects were almost 6 times as likely to have lower levels of vitamin D than subjects with a healthy weight (p = 0.0064); subjects who consumed milk sometimes versus regularly were 20 times more likely to have more hypovitaminosis D (p = 0.0001); compared to the summer, subjects measured in the fall were 6.9 times more likely to have lower levels of vitamin D (p = 0.0007); subjects who did not take a vitamin D supplement were 14 times more likely to have hypovitaminosis D (p = < 0.0001). There was no statistically significant relationship between gender and hypovitaminosis D

(p = 0.3026). Table 5 describes the factors that influenced the odds of having more severe hypovitaminosis D.

Table 5

Intercorrelations and predictors of hypovitaminosis D

Variable	*Adjusted OR*	*SD*	95%CI	*p*
Genotype				
Hgb SS vs Hgb SC	3.07	1.50	[1.18, 8.00]	0.0216
Hgb SC vs Hgb Other	2.48	1.93	[0.54, 11.41]	0.2421
Hgb SS vs Hgb Other	7.62	5.93	[1.66, 35.02]	0.0090
Gender				
Male vs female	1.61	0.75	[0.65, 4.00]	0.3026
Age				
1-5 vs 6-10	0.55	0.41	[0.12, 2.36]	0.4213
6-10 vs 11-15	0.11	0.07	[0.03, 0.40]	0.0007
11-15 vs 16-20	0.72	0.43	[0.22, 2.30]	0.5746
BMI				
Healthy weight vs overweight	6.23	4.12	[1.71, 22.75]	0.0056
Overweight vs obese	0.96	0.72	[0.22, 4.19]	0.947
Milk preference	11.10	10.26	[1.81, 67.98]	0.0093
No vs sometimes				
No vs yes	10	17.02	[0.36, 281.17]	0.1761
No vs sometimes, yes	292.14	551.49	[7.22, 11815.72]	0.0026
Sometimes vs yes	54.05	94.41	[1.76, 1658.38]	0.0097
Season	29.21	24.74	[5.55, 153.62]	<0.0001
Fall vs spring				
Fall vs summer	4.18	2.48	[1.31, 13.37]	0.0158
Winter vs fall	6.94	3.96	[2.27, 21.25]	0.0007
Spring vs summer	2.79	3.09	[0.32, 24.47]	0.3546
Winter vs spring	1.66	0.93	[0.56, 4.95]	0.3618
Winter vs summer	11.67	13.78	[1.15, 118.04]	0.0375
Vitamin D supplements	19.38	22.15	[2.06, 182.11]	0.0085
No vs yes	14.95	9.59	[4.25, 52.58]	<0.0001

Note: *OR* = odds ratio; CI = confidence interval

Ordinal logistic regression analysis was also used to evaluate the intercorrelations between hypovitaminosis D categories and ACS admissions. The data analysis revealed that subjects with vitamin D levels within the insufficient range were 17 times more likely to be hospitalized for this comorbid condition than those with serum 25(OH) D levels in the sufficient range (p = 0.0091). There were no statistically significant findings between the severe vitamin D

deficiency versus deficient categories (p = 0.7190), or between the deficient of insufficient vitamin D categories (p = 0.1845) (Table 6).

Table 6

Predictors of acute chest syndrome admissions according to Vitamin D category

Variable	*Unadjusted OR*	*SD*	95%CI	*p*
Vitamin D category				
Severe vs deficient	0.81	0.47	[0.26, 2.55]	0.7190
Deficient vs insufficient	0.53	0.25	[0.21, 1.35]	0.1845
Insufficient vs sufficient	17.77	19.60	[2.05, 154.21]	0.0091

Note. OR = odds ratio; CI = confidence interval

Ordinal logistic regression analysis was used to investigate the predictors of hospitalizations due to VOC pain crisis. Intercorrelations associated with the vitamin D categories and admissions for pain were examined with findings that indicated no significant relationship. However, there was a statistically significant correlation between pain admissions among the 1-5 versus 6-10 year old age group (p = 0.0410) (Table 7).

Table 7

Predictors of pain admissions according to vitamin D category

Variable	*Unadjusted OR*	*SD*	95%CI	*p*
Vitamin D category				
Severe vs deficient	2.54	1.66	[0.71, 9.14]	0.1526
Deficient vs insufficient	0.79	0.37	[0.31, 2.00]	0.62
Insufficient vs sufficient	8.08	6.88	[1.52, 4.28]	0.0141

Note. OR= odds ratio; CI= confidence interval

To examine the predictors and intercorrelations of inhaled corticosteroids strength associated with vitamin D categories, an ordinal logistic regression analysis was employed. This was a sub-population analysis related only to those identified as having a diagnosis of asthma. A statistically significant relationship was revealed between patients who were vitamin D deficient

who required lower doses of inhaled corticosteroids compared to those who had sufficient levels of vitamin D (p = 0.0090) (Table 8).

Table 8

Predictors of inhaled corticosteroid strength according to vitamin D category

Variable	*Unadjusted OR*	*SD*	95%CI	*p*
Vitamin D category				
Severe vs deficient	6.31	7.48	[0.62, 64.40]	0.1199
Deficient vs insufficient	0.10	0.09	[0.02, 0.56]	0.0090
Insufficient vs Sufficient	3.43	3.90	[0.37, 31.75]	0.2765

Note. OR = odds ratio, CI = confidence interval

Summary of Findings

One hundred and four children and adolescents with SCD underwent serum 25(OH) D screening according to the sites' Health Maintenance Prevention Guideline to identify the prevalence and correlates associated with hypovitaminosis D. The majority of the population had Hgb SS (55.8%), were male (52.9%), with a mean age of 11 years, who resided in an urban setting (77.9%). The bulk of the subjects were found to have a healthy BMI (67.5%). Most of the subjects were identified with skin type VI (59.6%), and 81.7% only consumed milk sometimes. Patients who took a vitamin D supplement (19.2%), had a median serum 25 (OH) D level of 26.5 ng/mL versus a median of 18 ng/mL among those who did not. Thirty-three percent had a diagnosis of asthma, of which 40% were prescribed a low dose of inhaled corticosteroids and 25.7% were prescribed a moderate strength inhaler. Over the last 5 years 46% of the subjects had at least one admission for ACS while almost 57% had at least 1 admission for VOC crisis. The overall prevalence of hypovitaminosis D among this cohort was 88.5%.

Among the biological factors, statistically significant associations with hypovitaminosis D included the following: Hgb SS, older in age, underweight, no preference for milk, and not

taking a vitamin D supplement. Neither gender nor skin type were found to have any statistical significance. Those with Hgb SS were 3 times more likely to have hypovitaminosis D than subjects with Hgb SC, and 7 times more likely than subjects with the other genotypes found in this cohort. No subject over the age of 10 years was found to have sufficient levels of vitamin D. Underweight individuals were about 6 times as likely to have hypovitaminosis D compared to those with a healthy weight.

A statistically significant environmental association revealed that those subjects screened in the fall were 3 times more likely to have hypovitaminosis D compared to individuals screened during the summer months. However, the subject's zip code status and corresponding population density was not found to be statistically significant.

Among the comorbidity variables investigated, there was a statistically significant correlation between hypovitaminosis D and subjects who had been admitted for an ACS episode. However, there was no statistical significant link between hypovitaminosis D and VOC crisis hospitalizations.

Regarding the medication variables, there was significant inverse relationship between those who took a vitamin D supplement and hypovitaminosis D. Those subjects who did not take a vitamin D supplement were 14 times more likely to have hypovitaminosis D compared to those who did use a daily supplement. Thirty-two of the 35 patients (91%) with a diagnosis of asthma fell in the hypovitaminosis D category. Sixty-five percent of these subjects with asthma are prescribed a daily inhaled corticosteroid. Chi square data analysis did not find a statistically significant association between inhaled corticosteroid strengths and vitamin D levels, however, an ordinal logistic regression revealed an inverse relation between lower inhaled steroid requirements among vitamin D deficient subjects compared to those with sufficiency.

Chapter 5
Discussion and conclusions

Discussion of findings

The purpose of this Quality Improvement Project, using a quantitative, cross-sectional, descriptive correlational design, was to identify the prevalence and correlates of hypovitaminosis D among children and adolescents with SCD enrolled at a non-profit tertiary children's hospital in southwestern PA. Additionally, a retrospective EHR review was conducted to examine intercorrelations between vitamin D levels and the subject's biological and environmental factors, medications and comorbidities. While the reviewed literature continues to link a variety of health disorders with hypovitaminosis D, the impact of this condition on children and adolescents with SCD remains limited.

This project demonstrated that hypovitaminosis D is a highly prevalent condition among a convenience sample of children and adolescents with SCD living in southwestern PA. Of the 104 subjects who had a serum 25(OH) D completed, almost 90% of the cohort had total vitamin D levels less than 30 ng/mL, over 1/3 were found to be insufficient (20 - 29 ng/mL), 39% had levels consistent with deficiency (10 - 19 ng/mL) and 17 (16.4%) subjects were identified as having severe vitamin D deficiency. Of note, only 3 patients (2.9%) were found to have detectable levels of vitamin D2 with a mean of 4.67 ± 1.33. To offer an interpretation of vitamin D2 levels found in the few subjects, 2 were prescribed vitamin D2 supplements and one patient with milk intolerance was given soy milk in lieu of cow's milk. Collectively, these findings serve to add to the accumulating results from other hypovitaminosis D prevalence studies conducted among pediatric SCD cohorts (Buison et al., 2004; Jackson et al., 2013; Rovner et al., 2008).

Other correlates may provide some insight as to the reasons why hypovitaminosis D is so prevalent among children and adolescents with SCD. The genotype Hgb SS has been investigated in several observational vitamin D studies which utilized a variety of biological, environmental, and comorbid correlates in relation to their vitamin D status with (Buison et al., 2004; Chapleon et al., 2009; Jackson et al., 2013; Rovner et al., 2008). However, to this researcher's knowledge, there are no prevalence studies that have included other genotypes. Since Hgb SS patients typically have a more severe course, it was not an unexpected finding that Hgb SS patients were more likely to have lower levels of vitamin D than Hgb SC. Nonetheless, these findings continue to add to the body of knowledge that there may be differences among the genotypes. Except for Hgb SC, due to the lack of variation and few numbers of subjects between the other genotypes (HgbS/β^+, HgbS/β^+ and 1 patient with *Xmn* 1 polymorphism), a statistical significance was not found and could not be interpreted.

Gender and age have also been examined in association with vitamin D levels in healthy unaffected children and pediatric sickle cell patients alike. However, since different age groups have been utilized between the studies, it is difficult to interpret any similarities with consistency. Nonetheless, the review of literature suggests that the female gender (Bentli et al., 2013) and an older age (Stein et al., 2006) may influence lower levels of vitamin D. Among the project's population, an older age was associated with lower vitamin D levels, but there was no significance between genders. Moreover, sufficient levels of vitamin D were only detected in those younger than 10 years. Possible explanations include: better diets that include more milk consumption in toddlers and younger children, worsening disease as one gets older leading to less outdoor activities to avoid temperature extremes, and less vitamin D being produced cutaneously with age.

Although conflicting, the literature has suggested both higher and lower BMI statuses have been associated with hypovitaminosis D. This project revealed that underweight subjects were more likely to have hypovitaminosis D than those with a healthy weight and overweight patients were more likely to have this condition than obese participants. Previous studies have suggested that impaired growth and poor nutritional status were common findings among pediatric SCD (Barden et al., 2002). Therefore it was an unexpected finding that the majority of this cohort were of healthy weight, and that almost ¼ of the subjects had BMI's greater than the 85th percentile. Perhaps this shift in the weight increase among children and adolescents with sickle cell parallels the increasing BMI's now found in the national populace.

The effects of cutaneous UVB exposure on vitamin D levels are decreased in those with darker melanin, including Hispanic and African Americans (Holick, 2004). While there was a trend noted among the different skin classifications, 62% of the subjects were identified with type VI skin pigmentation, and this may have led to not enough variation between the skin tones to test if the association was statistically significant. Although there was a six-fold greater likelihood that subject screened in the fall had lower levels of the vitamin D compared to those tested in the summer, the seasonal variation during the winter may have shown a greater impact on hypovitaminosis D had more subjects been screened during this time period.

Since very few naturally occurring foods contain vitamin D, governmental prevention strategies to ensure adequate intake of this vitamin have been largely accomplished through fortification of foods (Holick & Chen, 2008). This project identified that the majority of children and adolescents with SCD only drank vitamin D fortified milk "sometimes." This finding may merit the notion that persons at greater risk of hypovitaminosis D are consuming these products less often (Calvo & Whiting, 2013). This, in addition to their presumed reduced level of outdoor

activity and lack of sun exposure, places the SCD population at greater risk for hypovitaminosis D (Rovner et al., 2008).

ACS and VOC crisis were the two comorbidity variables of interest. To this researcher's knowledge, there has been only one other study to investigate a link between ACS and pain events in which no relationship was found (Jackson et al., 2013). In the current project, while ACS admissions had a higher predictability associated with hypovitaminosis D, hospitalizations for pain was not a significant finding. Although there is a well-known link between bone pain, muscle discomfort and chronic pain associated with hypovitaminosis D in the general public (as cited in Jackson et al., 2013) and some studies have shown a relationship between chronic pain and low levels of vitamin D in SCD (Osunkwo et al., 2011), this project found no link between these hypovitaminosis D and VOC crisis hospitalizations.

Asthma is a common co-morbid condition among patients with SCD. Despite convincing evidence that lower levels of vitamin D may be a predictor of asthma severity (Iqbal & Freishtat, 2011) or poorer lung function (Jackson et al., 2013), this project used an indirect measurement of asthma severity by correlating inhaled corticosteroid strength and hypovitaminosis D levels. Results revealed an unexpected predictor. Intercorrelations between vitamin D categories and inhaler strength showed that vitamin D deficient subjects were prescribed lower strengths of inhaled corticosteroids compared to subjects with sufficient D levels. One explanation could be related to lack of variability between these two groups. This inconsistency may also be related to poor pulmonology follow up, preventing adjustment of dose based on current pulmonary function tests.

Almost 20% of this population had either been previously prescribed a vitamin D supplement from another provider, or was using an over the counter supplement. While those

subjects taking supplements had an associated protective benefit against severe vitamin D deficiency (< 10 ng/mL), 65% still had hypovitaminosis D. Adherence to the vitamin D supplements was not assessed. Additionally, most over the counter products contain 400 IU's. Given that 65% of the population continued to exhibit hypovitaminosis D, perhaps patients with a chronic illness such as SCD have higher requirements.

There still remain inconsistencies among vitamin D experts between what constitutes severe deficiency, deficiency, insufficiency and sufficient levels of circulating vitamin D. The value ranges that were chosen for this project are in line with the Endocrine Society's (Holick et al., 2011) rather than the IOM (2011) recommendations, as the former's guidelines haves lower thresholds for what is classified as hypovitaminosis D. This researcher viewed this as a more preventative approach.

Limitations

There were limitations present in this project. This Quality Initiative project was a cross-sectional exploration of the prevalence and correlates of vitamin D among a small convenience sampling of pediatric sickle cell patients and therefore, causation cannot be concluded. Findings may not be generalizable to all children with SCD. A retrospective EHR review was conducted, and therefore the reporting of BMI, hospital admission diagnoses, and zip code status may not be reliable. The retrospective EHR review which included ACS and pain crisis admissions included only the previous 5 years, assuming that hypovitaminosis D had been present since that time. Although the Fitzpatrick's Skin Classification is a widely used tool in the dermatology field, the rating scale is a subjective assessment of skin color.

Although the sample population provided some heterogeneity between the genotypes, Hgb SS and Hgb SC, there were too few subjects with HgbS/β^+ (n = 8) and HgbS/β^0 (n = 3) to

allow for any significant inferences to be made. Only one subject had the mutation *Xmn*1 polymorphism which can serve to ameliorate the disease process. Therefore, potential confounding variables associated with vitamin D levels may include the phenotypical expression of disease severity, socioeconomic status and the ability to afford vitamin D fortified foods, in addition to lactose intolerance, which is found among some African Americans. The number of subjects that were screened in the winter (4.8%) were fewer in comparison to spring (27.8%), summer (33.7%), and the fall (33.7%). Results of this project found the mean 25(OH) D level in the fall was 17 ng/mL, the seasonal variation during the winter may have shown a greater impact on hypovitaminosis D had more subjects been screened during this timeframe. Although the LC/MS assay is the preferred method for analyzing total vitamin D due to its high specificity, performing this analysis requires a skilled technician (Vogeser, 2010). Potential hydroxyvitamin D quantification errors could have occurred in the sample population leading to another limitation in the project. Due to these factors, conclusions should be made with caution.

Implications

There is increasing concern over the global prevalence of hypovitaminosis D and growing evidence of its associated health conditions. While health care expenditures for children and adolescents with SCD can be up to 11 times higher in comparison to children without SCD (Amendah, Mvundura, Kavanagh, Sprinz, & Grosse, 2010), with an estimated lifetime medical costs averaging to $460, 151 per individual (Kauf, Coates, Huazhi, Mody-Patel, & Hartzema, 2009), increasing interest should be channeled toward investigating alternative adjunct modalities to prevent further disabling conditions among this population. Therefore, the nurse practitioner's role should be aimed at preventing potential comorbidities that may be associated

with hypovitaminosis D by implementing well-designed early screening programs, coupled with nutritional support, education, and treatment if needed.

Education.

It is important for the nurse practitioner to educate patients and families about the 3 ways in which to optimize their vitamin D status through sun exposure, naturally occurring foods or fortified food sources and vitamin D supplements. Subjects in this project who reported consuming milk regularly had a higher likelihood of having increased levels of circulating 25(OH) D than those who only drank milk sometimes. For subjects who do not drink milk at all, consuming orange juice fortified with vitamin D may be an alternate solution. However, a more inclusive approach may consist of instructions on consuming proper vitamin D food sources and serving sizes, but also encouraging sensible sunshine exposure and taking a vitamin D supplement as part of a prevention and treatment regimen to combat hypovitaminosis D among children and adolescents with SCD.

Policy.

As the connection with hypovitaminosis D and other health conditions have been conducted largely through observational studies, further investigation among the general public, and in SCD specifically is warranted. Currently, the ideal amount of vitamin D intake to prevent hypovitaminosis D and related health problems remain unclear as the vitamin D experts disagree on daily requirements. Vitamin D policy recommendations and guidelines will only come to fruition though scientific evidence. The cause and effect relationship that hypovitaminosis D poses on health conditions require prospective, longitudinal studies on multiple populations, with a variety of illnesses, across the life span.

Advocacy.

While vitamin D has been historically linked to calcium and bone health, current concerns about the increasing prevalence of hypovitaminosis D over the last few decades has prompted research to examine its health effects beyond the skeletal boundaries. Although curative therapies for SCD have improved over the last decade, options to become the recipient of a bone marrow transplant for this genetic disorder are few. As a result, there is an increasing interest in the potential adjunct modalities that early screening, prevention, nutritional support, education, and treatment can lend. This accumulating body of literature has as its aim, to advocate for alternative strategies as a means to diminish disease comorbidities in hopes of preventing further disabling symptoms and improving quality of life. Another important role of being an advocate is to continue to learn and maintain a current knowledge base, and to be able to educate patients and families on new information and treatment options as they become available with hypovitaminosis D being a good example. Promoting awareness through these means can have important primary, secondary and tertiary prevention implications which may lead to less disabling conditions and better health outcomes.

Recommendations for further practice and for further study.

The current recommendations for vitamin D prevention and screening practices studies are vague. Although African Americans have been identified as a population at risk, observational studies have shown that individuals with SCD are at even higher risk. As this project revealed, there is a high prevalence of hypovitaminosis D among children and adolescents with SCD who reside in southwestern PA. It is therefore recommended that health maintenance and prevention guidelines designed for pediatric patients with SCD have a low threshold of suspicion for hypovitaminosis D occurring in this population. Further research is

warranted to define the optimal range of circulating vitamin D and a sufficient daily requirement for patients with SCD. Additionally, it will be important to determine if vitamin D status improves clinical outcomes among this population. Until then, maintaining adequate serum 25(OH) D among children and adolescents with SCD would be a practical strategy.

The connection between hypovitaminosis D among children and adolescents with SCD who were older, underweight, having Hgb SS genotype, reporting little or no milk consumption, and screened in the fall or winter suggests that careful notice should be given to either optimize the patient's vitamin D intake through diet education or supplementation or a combination of these two. Multi-center studies that investigate the correlates of hypovitaminosis D in pediatric SCD may provide more clearer and representative results. In the meantime, early prevention of hypovitaminosis D thorough screening with serum 25(OH) D among patients with SCD may represent an opportunity to improve their health outcomes while treatment plans should be individually tailored to consider each patient's biological, environmental, comorbid and medication factors.

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Appendix A

UPMC Quality Improvement Committee Approval

The data outcomes of this project will only be applicable to the population at Children's Hospital of Pittsburgh. The findings will be unique to this population only and are not intended to be generalized outside of this institution. This project does not include any prospective data to compare interventions. The project coordinator who already provides care and treatment to this population will be the only person to review retrospective medical records. The vitamin D level will be drawn at the same time as the patients scheduled lab work so to avoid an additional venipuncture. The goal of the project implementation is to improve our standard of care and clinical practice and prevent potential adverse outcomes as evidenced by the review of literature which has shown that this population is at risk for inadequate levels of vitamin D.

Completed forms are to be submitted electronically) to:
Karen Anderson in the Office of Medical Affairs,
CHP who will then forward to Dr. J. Jegasothy

For completion by QI Review Committee Designee: This section is for committee use only.

Date of Review: 11/20/14 Date Approved: 11/26/14

Approved as Quality Improvement Project:

Agree: ☐X

Disagree: ☐

Date to be presented to Total Quality Council: Copy to QI leadership

Prospective date for feedback to TQC on outcomes:

Comments: This is a project using retrospective reviews and patient questionnaires to evaluate the impact over the last 6 months of a newly implemented evidence based testing guidelines for Vitamin D deficiency as standard of care in pediatric sickle cell disease. The goal of the project is to improve standard of care and clinical practice and prevent potential adverse outcomes as evidenced by the review of literature which has shown that this population is at risk for inadequate levels of vitamin D. This is approved as a Quality Improvement project.

QI Review Number: 0001904 Completed
by: Dr. J. Jegasothy

Appendix B

Carlow University Internal Review Board Approval Letter

CARLOW UNIVERSITY
Values. Scholarship. Vision.®

CARLOW UNIVERSITY
INSTITUTIONAL REVIEW BOARD

TO: Patricia McLendon, CRNP
Peggy Slota, DNP

FROM: Robert A. Reed, Psy. D.
Co-Chair, IRB

DATE: December 22, 2014

RE: Study # 14-079-G-213 Vitamin D Deficiency in Pediatric Sickle Cell Disease

The above proposal is approved as a Quality Improvement project, based on the information you have provided. Projects reviewed and approved by Carlow University IRB as a Quality Improvement project do not meet the federal definition of research according to 45 CFR 46.102(d) and do not require additional IRB oversight. However, this proposal may be subject to other state, local or institutional regulations, policies or requirements.

The project is approved for a period of up to one year.

Approval Date: December 22, 2014

Expiration Date: December 21, 2015

If any untoward incidents should develop in the course of your project or if you have questions or need further assistance, please contact the Institutional Review Board Office at 578-6349.

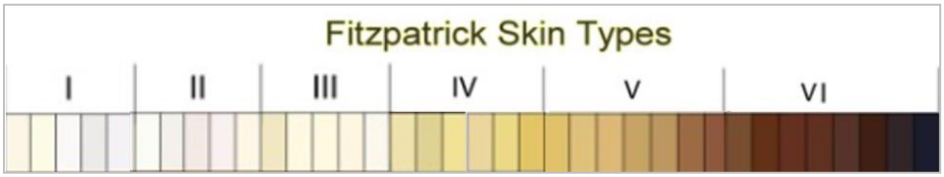
Appendix C1

Fitzpatrick Skin Color Classification Scale

Skin Type	Skin Appearance	Tans
Type I	Pale, ivory	No
Type II	Fair skinned	Lightly
Type III	Light to medium	Average
Type IV	Medium, beige, olive	Yes
Type V	Medium bronze to brown	Yes
Type VI	Dark brown to black	Yes

Appendix C2

Fitzpatrick Skin Tone Visual Chart Adapted from HTetronics



Appendix D

Vitamin D Correlates Tool

Pt ID	**Season** Spr Summ Fall Witer	**Geno -type** SS, SB0, SB+, SC other	**Gen-der**	**Age**	**BMI** Under Health Over Obese	**Skin** 1-6	**ICS** None Low Mod	**ACS** Last 5 yrs	**VOC** Last 5 yrs	**Likes Milk** Yes Some-times No	25 OH D Tot	D3	D 2	Vit D Sups	**Zip code**	Pop Den sity Urb Rur
1	Spr	SC	M	15	obese	6	None	0	0	S	10	10	< 2	no	15216	Urb
2	Spr	SS	F	15	under	6	None	1	2	S	5	5	< 2	no	15090	Urb
3	Spr	SS	M	5	under	5	Low	3	1	S	5	5	< 2	yes	15208	Rur