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Prevalence of vitamin D deficiency in children with sickle cell anemia: a systematic review

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Abstract

Sickle cell anemia is a genetic disease that is highly prevalent in the Brazilian population, especially among black ethnic groups descended from migration of enslaved people from Africa, as well as descendants from the process of miscegenation. The disease is a clinical expression of the homozygosity of the hemoglobin S gene, which may be of genetic and/or hereditary origin, and is caused by the replacement of the normal residue of glutamic acid with the amino acid valine in the sixth position of the polypeptide chains of the beta-globin protein. This process generates biochemical alterations in hemoglobin S molecules that polymerize inside the erythrocyte and transform into sickle cells. Lack of vitamin D may possibly be linked to disease processes, as well as to individuals' pain crises. Objectives: To conduct a systematic review in order to analyze the prevalence of vitamin D deficiency in children with sickle cell anemia. Methodology: A systematic review was carried out by means of a search for original articles in the English and Portuguese languages in the following scientific databases: Pubmed, Science Direct, Lilacs and Scielo. Results: Among 10 articles found, 8 showed a prevalence of vitamin D deficiency (<20 ng/mL) in children with sickle cell anemia. Conclusion: The prevalence of vitamin D deficiency was high in patients with sickle cell disease, so supplementation of this substance may be helpful in treatments to improve the condition and in preventing deficiency. However, further studies that target this association and/or intervention are required to obtain more practical results.

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Introduction

The identification of nutritional status through diagnostic procedures is essential for the diagnosis of possible nutritional disorders of individuals and/or the population, in addition to the establishment of degrees of risk, as well as causal and nutritional factors.[1]

According to Mataratzis and colleagues,[2] sickle cell anemia (SCA) is characterized by a prevalent homozygous form of hemoglobin S, that is, it is characteristic of individuals who receive an abnormal hemoglobin S gene from the father and another from the mother. To be considered a trait anemia, the patient must receive a gene for normal hemoglobin (A) and another for abnormal hemoglobin (S), thus becoming a carrier of sickle cell anemia trait (AS). In Brazil, this disease varies by region, with higher rates in the Northeast, due to a high prevalence of descendants of Africans. On average, 3,500 children are estimated to be born with sickle cell disease every year in Brazil, to such an extent that it is considered a public health problem.

Approximately 5% of people in the world carry genes responsible for hemoglobinopathies in their structure, with an estimated 5,476,407 children born with sickle cell trait (SA) and 312,302 with HbSS worldwide every year. In underdeveloped countries, such as those of sub-Saharan Africa, the estimated number of live births with the HbSS gene is 235,681 births per year. This number is much higher than in developed countries, such as the United Kingdom, which has a rate of 300 births; and the United States of America (USA), with approximately 3,000 births.[3]

Patients with sickle cell anemia are initially asymptomatic in the first six months of life due to the presence of fetal hemoglobin (HbF), whose concentrations are higher than those of adults. Even so, this pathology is associated in childhood with high incidences of morbidity and mortality due to sepsis, splenic sequestration, aplastic crisis, acute chest syndrome and stroke.[4]

According to Hankins,[5] chances of survival can be increased in children exposed, at an early stage, to simple measures: early diagnosis, anticipatory guidance, prophylactic treatment and implementation of neonatal screening programs, including neonatal screening and preventive pediatrics, linked to genetics.[6]

Since the disease is transmitted through a genetic factor, genetic counseling is considered to be of crucial importance, in order to provide guidance both to patients about traits of the disease as well as to those in which the disease is already developed. Counseling helps to enhance the reproducibility and understanding of certain aspects of the disease, such as suffering, treatment and prognosis. This genetic counseling is of an auxiliary nature, providing guidance to individuals and families of individuals with the pathology. For the purposes of this counseling, it is necessary to establish whether the patient is a homozygote or a heterozygote, and hemoglobin S must be confirmed and differentiated from other hemoglobins.[7]

Salles and colleagues[8] state that children with sickle cell anemia may develop airway obstructions and even hypertrophy, with a prevalence of 55.3% of obstruction being observed. This condition may be associated with obstructive sleep apnea syndrome as well as contribute to episodes of hypoxemia. One of the most important characteristics of the disease is the vaso-occlusive crisis, also known as sickle cell crisis, resulting in the obstruction of small blood vessels, tissue hypoxia, necrosis, and severe pain. Strokes and chronic hemolytic anemia are also common.

Sickle cell anemia is a chronic and incurable disease that is amenable to treatment, but even so, inflicts a great degree of suffering on its carriers, who merit special attention from the den-

tal, medical, psychosocial and genetic points of view. The obstruction of blood vessels generates pain crises, with swelling and necrosis in various organs, such as bones and joints, spleen, lungs and kidneys.[9]

According to studies, calcium and vitamin D are involved in the bone metabolism, such that low calcium intake leads to a reduction in the ideal bone mass peak among children and adolescents, constituting an aggravating or determining factor of impaired growth in children and adolescents with sickle cell anemia. Deficiencies in these substances lead to fragility and bone deformities, such as rickets, which is a classic condition derived from the lack of these micronutrients, according to studies that have examined dietary inadequacy.[2]

Vitamin D

According to Castro,[9] the term vitamin D encompasses a group of secosteroid molecules derived from 7-dehydrocholesterol (7-DHC) that is interconnected through various photolytic and enzymatic reactions occurring in cells of different tissues. These substances thus cover both active metabolisms (1 to, 25-dihydroxyvitamin D or calcitriol) and their precursors (vitamin D3 or cholecalciferol, vitamin D2 or ergosterol and 25-hydroxyvitamin D or calcidiol), as well as products of their degradation, which may still maintain some metabolic activity.

In humans, only 10 to 20% of the necessary vitamin D comes from our diet. The main dietary sources are vitamin D3 (cholecalciferol, of animal origin), which is present in fatty fish from cold and deep waters, such as tuna and salmon, and vitamin D2 (ergosterol of vegetable origin), which is present in edible fungi. The remaining 80% to 90% is synthesized endogenously.[10]

According to Alves and colleagues,[11] the role of vitamin D is to regulate the phosphocalcic metabolism, in order to ensure bone mineralization functions. It is the only vitamin that can be synthesized by the skin from exposure to sunlight (ultraviolet radiation).

The vitamin obtained from ultraviolet irradiation is D3, as sunlight hits the skin and forms pro-vitamin D3, which in contact with the skin is transformed into pre-vitamin D3. Both D2 and D3 can also come from the diet. In the metabolism, the substance subsequently undergoes hydroxylation in the liver by 25-hydroxylase and becomes 25-hydroxyvitamin D. This process requires additional hydroxylation in the kidney by 1 alpha-hydroxylase to then form the biologically active form of vitamin D 1,25-dihydroxyvitamin D.[11]

According to Nolan and colleagues,[12] vitamin D (25-hydroxyvitamin D) deficiency has emerged as a public health issue in recent years due to its contribution to skeletal and extra-skeletal manifestations. Individuals with sickle cell disease reportedly tend to present a high prevalence of vitamin D deficiency.

Among the vitamins, according to Oliveira and colleagues,[13] vitamin D should be carefully evaluated in children and adolescents with sickle cell anemia, since low amounts occur due to the high concentration of melanin in the skin, reduced levels of physical activity and low food intake, all of which contribute to the development of the deficiency.

According to Soe and colleagues,[14] the increase in catabolism can generate an energy deficit and even nutrient absorption, so that those who present this pathology can suffer from multiple deficiencies of macronutrients and micronutrients. Among these is vitamin D, which is responsible for calcium homeostasis and also essential for bone mineralization, such that vitamin D deficiency may harm skeletal muscles.

According to Oliveira and colleagues,[13] for Dietary Reference Intakes, vitamin D deficiency occurs when the serum concentration of 25-hydroxyvitamin D is lower than 11ng/mL, and is possibly also related to the pain crises of individuals with the sickle cell disease, although no studies have been able to link the two phenomena.

Still, according to Alves and colleagues,[11] when a sufficient amount of vitamin D is present, more phosphorus and calcium is absorbed, so that osteoblasts can use 1,25-dihydroxyvitamin for D to interact with the vitamin D receptor, inducing immature monocytes to become mature osteoclasts and dissolve the matrix, thereby fixing calcium and other skeletal minerals.

According to Adegoke and colleagues,[15] vitamin D (D3) supplementation can serve as an anti-inflammatory substance in the treatment of sickle cell disease. However, they consider the number of studies on the subject to be somewhat low, since some articles about children refer to an extra supplementation of vitamin D3 of 2000 IU per day, over a period of three months, thus generating an increase in cytokines.

In addition, Arya and colleagues,[16] in a case report study that associates chronic pain with sickle cell disease, showed that vitamin D supplementation through intramuscular injection of 600,000 IU (15 mg) of cholecalciferol (vitamin D3) can be suitable for the relief of chronic pain, subject to accompanying laboratory tests.

Brazil has high rates of sickle cell anemia, especially among individuals of African descent, leading the disease to be considered a public health problem.

Nutritional status is known to be a major aggravating factor for the disease, and must be taken into consideration during treatment. Vitamin D is one of the vitamins that may be associated with this pathology, thus presenting possible deficiencies, and may be correlated with pain crises in individuals if it is not ingested in correct amounts.

In light of these considerations, the present study seeks to analyze the prevalence of vitamin D deficiency in children with sickle cell anemia, through a systematic review, in order to shed light on possible associations between the two conditions.

Methodology

A systematic review was carried out by means of a search for original articles in English and Portuguese, published during the last 12 years. The search sought to identify the prevalence of vitamin D deficiency in children with sickle cell anemia. The scientific databases used were: Science direct, Pubmed, Medline, Scielo and Lilacs. Scientific journals and journals available in electronic format were also used.

The descriptors used in Portuguese and in English were: “sickle cell anemia”, “nutritional status of children with sickle cell anemia”, “sickle cell anemia as public health problem”, “prevention and sickle cell anemia”, “symptoms and sickle cell anemia”, “treatment and sickle cell anemia”, “vitamin D”, “vitamin D and sickle cell anemia”, “vitamin D deficiency in children with sickle cell anemia”, “prevalence of vitamin D deficiency in children with sickle cell anemia”, and “vitamin D deficiencies in sickle cell anemia.”

The inclusion criteria for conducting the systematic review were initially a search for articles according to the titles and abstracts analyzed. The search focused on studies that dealt with children while also presenting the amounts of vitamin D deficiency among the participants,

thus showing possible associations with the pathology of sickle cell anemia. After an electronic search, priority was given to the most recent publications.

Research unrelated to the topic, literature reviews, and animal studies were excluded, and a critical analysis was performed of each of the selected studies, in order to assess the validity of the results obtained and the possibility of conclusions being based on correlated data.

Results

Table 1 presents the articles selected for the present study, describing author, year, location; sample number; mean age; vitamin D dosage; p-value; duration and type of study; and adequacy of vitamin D deficiency in relation to the established dosage.

Table 1. Data collection of children with sickle cell anemia x adequacy and/or inadequacy of vitamin D.

Author, year and place	Sample size	Mean age	Vitamin D dosage	*P***	Duration and type of study	Results of vitamin D deficiencies
Adegoke et al, 2017 (Nigeria)[15]	170	7 years	>=30ng/mL	*P*>0.05	12 months Transversal	Negative
AlJama et al, 2018 (Saudi Arabia)[17]	640	12 years	<20ng/mL	*P*<0.05	5 years Transversal	Positive
Jackson et al, 2012 (USA)[18]	139	11.5 years	<20ng/mL	*P*<0.05	4 years Transversal	Positive
Rovner et at, 2008 (USA)[19]	150	11.5 years	<20ng/mL	*P*<0.05	1 year Student's T-Test	Positive
Wykes et al, 2014 (London)[20]	81	9,8 years	<20ng/mL	*P*<0.05	NR	Positive
Garrido et al, 2012 (Spain)[21]	78	4.3 years	<20ng/mL	*P*<0.05	3 years Transversal	Positive
Adegoke et al, 2017 (Nigeria)[22]	123	8 years	>=30ng/mL	*P*>0.05	NR Transversal	Negative
Adegoke et al, 2016 (Brazil)[23]	36	7.5 years	<20ng/mL	*P*<0.05	NR Cross-sectional Prospective	Positive
Lee et al, 2015 (Colombia)[24]	95	10.6 years	<20ng/mL	*P*<0.05	1 year e 4 months Transversal	Positive
Osunkwo et al, 2011 (NR)[25]	53	12 years	<20ng/mL	NR	2 years NR	Positive

Legend: NR: Not Reported.
Source: The authors (2022).

According to the study by Adegoke and colleagues[2] carried out in Ile-Ife, Nigeria, using data collected from 170 patients over a period of twelve months in children with a mean age of 7 years, 2 of whom were diagnosed with vitamin D deficiency (<20ng/mL), 12 with insufficiency (<30ng/mL) and 156 with sufficient levels (>=30ng/mL), while 95 of these children had sickle cell anemia in a steady state, that is, the period during which the child is free from pain, infection and/or any other illness, while 75 children were apparently healthy.

The result of this experiment established that the means of both groups were similar and the serum pro-inflammatory cytokines measured during the study of children with suboptimal vitamin D (<30ng/mL) were significantly higher than those in children with normal serum vitamin D (>=30ng/mL), such that the cytokines showed increased values in children with sickle cell anemia compared to healthy ones. Although the study found two children diagnosed with deficiency and 12 with insufficiency, most children obtained adequate levels of vitamin D, indicating a negative result for vitamin D deficiency.[2]

Another study, by AlJama and colleagues,[17] was carried out over a period of 5 years in the Eastern Province of Saudi Arabia, in the city of Al-Qatif, in which 640 children were monitored, with a mean age of 12 years, and vitamin D deficiency being confirmed by hemoglobin electrophoresis, independently of the status of the disease, through the performance of a vitamin D reading. The 49 children with sickle cell anemia had 25-OH-D levels of 16.3ng/mL, 463 children with sickle cell anemia in crisis periods had levels of 10.1ng/mL and 128 children without seizures had levels of 15.7ng/mL, which are considered to be extremely low amounts of vitamin D.

As a result, the mean level of 25-OH-D was statistically higher in the group of patients diagnosed with sickle cell anemia in pain crisis, but vitamin D levels were insufficient and deficient in all groups, in such a way as to present values of inadequacy. The study thus demonstrated a positive relationship between vitamin D deficiency with sickle cell anemia in children.[17]

In addition, Jackson and colleagues[16] carried out another study with 139 children diagnosed with sickle cell disease, with a mean age of 11.5 years, which evaluated seasonal issues related to vitamin D levels. The results showed that 96.4% of the children had vitamin D deficiency (<20ng/mL), 64% had severe deficiency (<10ng/mL), the levels of 1.4% were insufficient (20.01–29.9ng/mL) and 2.2% showed sufficient (>/30ng/mL) vitamin D. Therefore, the analysis of the results confirmed the pertinent vitamin D deficiency, although full multivariate models did not find significant associations of severe vitamin D deficiency (<10ng/mL) with episodes of pain attacks.

In the same line of study and using Student's T Test, Rovner and colleagues[19] analyzed 150 children diagnosed with sickle cell disease, with a mean age equal to that of the previous study. Of the individuals analyzed, 61 African-Americans with the condition had deficient serum 25-OH-D levels (15ng/mL) and 89 healthy African-American control subjects had insufficient serum levels (21ng/mL). The study found that vitamin D deficiency was 5.3 times higher in children with sickle cell anemia, signaling a positive association.

In addition, Wykes and colleagues[20] analyzed the prevalence of vitamin D deficiency and its pathophysiological correlates in 81 children with a median age of 9.8 years, through measurement of 25-OH-D by blood tests. Of the children participating in the study, only 1 had sufficient 25-OH-D (>=30ng/mL), 6 had insufficient levels (21-29ng/mL) and 74 showed deficiency (<20ng/mL). As a result, the widespread presence of vitamin D deficiency was confirmed. The age of the children was significantly correlated with deficiency levels, tending to decline as age increased, with a correlation between 25-OH-D levels and serum calcium levels.

In the study by Garrido and colleagues,[21] 78 African, African-American and Asian children, with a mean age of 4.3 years, diagnosed with sickle cell anemia and vitamin D deficient status, were analyzed in a 3-year cross-sectional study. Of the children analyzed, 56% had vitamin D deficiency values of 25(OH)D below 20ng/mL, with this percentage increasing to 79.5% when

considering 25(OH)D levels below 30ng/mL as insufficient, while 17.9% of individuals had 25(OH)D levels below <11ng/mL. The study found a high prevalence of insufficient and deficient levels of vitamin D in patients with sickle cell anemia.

In addition, Adegoke and colleagues[22] carried out a study with 123 children diagnosed with sickle cell disease, in order to verify the influence of serum 25-OH-D on episodes of acute pain in Nigerian children with a median age of 8 years. The study found that 14 children had deficient 25-OH-D levels (<20ng/mL), while 109 had sufficient levels (>=30 ng/mL), and none of the children presented severe vitamin D deficiency. Ninety children with sickle cell disease had at least one significant pain crisis, such that the frequency of pain was inversely correlated with the serum level of 25-OH-D, although this result was not statistically significant.

In another prospective cross-sectional study, Adegoke and colleagues[23] analyzed 36 children with a mean age of 7.5 years, under treatment at the Pediatric Hematology Clinic at the Federal University of São Paulo, diagnosed with sickle cell anemia and probable vitamin D deficiency associated with hemolysis biomarkers. Of the participants, 23 had sufficient levels of vitamin D (>=30ng/mL) and 13 had deficient levels (<20ng/mL). In this context, analysis of the relationship between serum vitamin D and hemolysis biomarkers showed that the mean hemoglobin of children with vitamin D deficiency was significantly lower than those without vitamin D deficiency. Therefore, this study can be considered positive in the face of vitamin D deficiency in patients with sickle cell disease, since the sample is small and a little less than half of the sample showed values below insufficient and sufficient.

The study by Lee and colleagues,[24] carried out in Colombia with 95 children with median age of 10.6 years, analyzed sickle cell anemia, vitamin D deficiency and acute vaso-occlusive complications over a period of 1 year and 4 months. The participants included 56 vitamin D deficient patients (<20ng/mL), 27 of whom were severely deficient (<10 ng/mL) and the status of 12 others was not reported. The result of this study was positive for vitamin D deficiency, since the mean level of 25-OH-D was 18ng/mL, with the lowest mean in spring (15.2ng/mL) and highest in summer (22.4ng/mL). However, overall, no significant differences were found across seasons. Significant associations made with the level of 25-OH-D and acute vaso-occlusive complications showed that 31 of these children had at least one episode of pain.

Osunkwo and colleagues[25] analyzed 53 children with mean age of 12 years, who had sickle cell disease, vitamin D deficiency and chronic pain. Of the participants, 15% had insufficient levels of vitamin D (21-29ng-mL), 32% were deficient (<20ng/mL), 40% severely deficient (<15ng/mL) and 13% profoundly deficient (<10ng/mL). A positive result of the study for vitamin D deficiency showed that 32% of children had the chronic pain and bone fragility associated with low levels of 25-OH-D.

Discussion

The term sickle cell disease (SCD) refers to a group of hereditary hemoglobinopathies resulting from a disorder in the morphophysiological morphology of hemoglobin (Hb). Among the types of DF, the genetic composition with the greatest clinical impact is sickle cell anemia disease (SCA), a condition in which the HbS gene is inherited from both parents and culminates in the homozygous form HbSS.[3]

The study presented by Samuel Ademola Adegoke and colleagues[2] demonstrated that the expression of cytokines with concomitant inflammation, cell adhesion to the vascular endotheli-

um and, consequently, endothelial injury, contributes to the process of vaso-occlusion in sickle cell disease. However, regarding the relationship between changes in cytokine levels and the pathophysiology of vaso-occlusive crisis, conclusions remain largely inconsistent.

This study also found that children with adequate levels of vitamin D (>=30ng/mL) had significantly higher levels of pro-inflammatory cytokines, with an inversely significant correlation with serum levels of 25-OH-D.[2]

This result stems from the fact that vitamin D has significant impacts on bone health and on the prevention of respiratory diseases, as well as hemolysis, thus contributing to the growing body of evidence about the preventive effects of vitamin D on immune disorders, since it triggers changes in the production of inflammatory cytokines and inhibits the proliferation of pro-inflammatory cells.[2]

These responses presented by vitamin D deficiency in patients with sickle cell disease are extremely important, since they result in bones being affected by microinfarcts, osteopenia, osteoporosis, osteomyelitis and osteonecrosis, as well as low bone mineral density. These conditions, as well as lack of exposure to sunlight, have been described in children with sickle cell anemia. Sunlight is considered essential for bone health, since approximately 90% of the necessary synthesis of vitamin D is derived from exposure to sunlight.[26]

Studies included in this review show that the onset of hypovitaminosis due to vitamin D in the general population of a sunny and dry country such as Saudi Arabia, for example, can approach 100%. This phenomenon leads to high rates of vitamin D deficiency in the population, insofar as to trigger a pandemic health problem, even in areas with sunshine all year round. This high incidence of vitamin D deficiency is more severe in children with sickle cell anemia in crisis. They are characterized by increased concentrations of inflammatory cytokines, which would explain the low levels of vitamin D during the sickle cell crisis, with symptoms of chronic pain observed both in cases of sickle cell disease and of vitamin D deficiency.[17] However, according to Alves and colleagues,[11] vitamin D levels can vary according to nutritional, genetic or even hormonal factors.

The high prevalence of severe vitamin D deficiency among children with sickle cell disease in different locations and latitudes may be related to cultural, behavioral, and environmental factors. Therefore, early screening for vitamin D deficiency is necessary to prevent bone mineral complications.[18]

Race, age, body mass index, latitude, diet, exposure to sunlight and skin pigmentation are all factors that influence the status of vitamin D. As well as its effects on bone health, vitamin D is associated with a variety of health conditions, including cardiovascular diseases, asthma, nephropathy and chronic pain.[12]

In addition, the concentrations of low vitamin D levels in 25-OH-D vary according to season and latitude. Its bioavailability, especially in winter, depends on diet and the body's hepatic reserves, and can lead to impaired intestinal absorption of vitamin D. Renal and liver abnormalities also play a role in vitamin D status in sickle cell disease.[27]

Another factor that may be significant for vitamin D production in sickle cell anemia is increased concentrations of melanin in the skin, particularly in African children, which is associated with reduced levels of physical activity and low vitamin D intake. Most African-Americans with sickle cell anemia tend to display this increase of melanin concentrations in the skin, so

they may not spend sufficient time outdoors to synthesize enough vitamin D, regardless of the geographic region in which they live.[19]

In light of the melanin concentrations, the nutritional factor undoubtedly influences the severity of the complications of the pathology , since the need for macro and micronutrients increases significantly due to the high metabolic demand caused especially by chronic hemolysis. The Basal Metabolic Rate (BMR) is 20% higher in children with sickle cell anemia compared to the population as a whole, because of increased catabolism.[28]

According to Wykes and colleagues,[20] vitamin D deficiency is considered common in sickle cell anemia, although the significance of its correction is not fully understood. Vitamin D is implicated in bone metabolism and in a wide range of physiological processes, as well as in the control of blood pressure, insulin secretion, lipid metabolism. Its deficiency is associated with the development of stroke, heart failure (HF), renal failure (RI), immunodeficiencies and even cancer. Severe deficiency in children causes rickets, osteomalacia with bone deformation, and may be associated with bone and muscle impairment, reduced growth and bone pain, so that low levels of the vitamin may result in a low absorption of sunlight, darkened skin, and food intake.

Mutational heterogeneity and genetic characteristics, as well as the environmental and social characteristics of individuals, are also factors that may be related to the clinical manifestations and complications of sickle cell disease.[29] According to Garrido and colleagues,[21] vitamin D deficiency is related to an increase in respiratory infections among children with sickle cell anemia and may also be related to increased skin pigmentation, reduced exposure to the sun and reduced intake of calcium and vitamin D. Vitamin D is highly important for bone health, but few articles analyze the risk of fractures in children with sickle cell anemia, so tests are necessary to assess the possible association between vitamin D levels and fractures.

Studies have shown that the serum 25-OH-D may influence the rate of significant episodes of pain in children with sickle cell anemia, suggesting a possible association between low levels of the serum and increased frequency of acute pain. Therefore, regular screening for vitamin D in children with suboptimal vitamin D levels is recommended, in conjunction with supplementation to reduce pain episodes.[22]

Another study, carried out by Samuel Ademola Adegoke and colleagues,[21] showed a correlation between decreases in hemoglobin and hematocrit levels after the reduction of serum 25-OH-D levels, suggesting a way in which vitamin D deficiency may play a role in the pathogenesis of the hemolytic phenotype of sickle cell disease. In patients with this pathology, hemolysis has been associated with reticulocytosis and endothelial dysfunction, triggering leg ulcers, pulmonary hypertension and stroke. Therefore, supplementation for these types of patients can be considered as standard procedure in order to improve health outcomes.

In addition, Martins30 has also shown that when the sickling of sickle cell anemia is formed, red blood cells begin to harden, and changes occur in membrane proteins and the expression of adhesion molecules increases. As a result, these red blood cells adhere to the endothelium, triggering an inflammatory phenomenon characterized by coagulation activation, hypoxia, ischemia, local infarction and reduced red blood cell survival. The repercussions of these alterations are responsible for the main signs and symptoms of sickle cell disease, such as pain, hemolytic anemia and progressive impairment of multiple organs, leading to morbidity and mortality.

Still according to Margaret and colleagues,[24] vitamin D deficiency is closely related to acute vaso-occlusive complications, which are associated with sickle cell disease in these individuals. These complications occur because patients with this pathology present a pro-inflammatory state with underlying microvascular obstruction and endothelial dysfunction, as well as vasculopathy induced by hemolysis and infections. Through its immunoregulatory and antimicrobial functions, vitamin D can help to control these processes and may help to reduce vaso-occlusive complications.

The study by Osunkwo and colleagues[25] showed that the peak effect on the reduction of days of pain occurred when serum levels of 25-OH-D exceeded 30ng/mL, indicating the possibility that vitamin D can also assist in pain reduction. Study findings confirm that individuals with sickle cell disease are particularly prone to vitamin D deficiency and suggest a link between this deficiency and bone fragility, demonstrating how vitamin D deficiency in children can lead to retarded growth and generate signs and classic symptoms of rickets, muscle weakness, which may also cause bone mineralization defects.[31]

Conclusion

This work aims to analyze, through systematic verification, the prevalence of vitamin D deficiency in children with sickle cell anemia, and concludes that the prevalence of vitamin D deficiency is high in patients with this pathology. Therefore, vitamin D supplementation may possibly serve as a means of treatment to improve the condition and prevent deficiency, and even decrease the frequency of pain crises. However, further clinical studies with larger sample sizes directly focused on this association and/or intervention are required.

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