RMMG
Revista Médica de Minas Gerais

REVIEW ARTICLE

Sickle cell disease and the modulating effect of vitamin D in children: an integrative review

Doença falciforme e o efeito modulador da vitamina D em crianças: uma revisão integrativa

Thaís Sette Espósito[1], Franciane Vilela Réche da Motta[2], Amanda do Carmo Gusmão[3], Andressa de Araujo Rodrigues Neto[4], Olivia Franco dos Santos[5], Rodrigo De Martin Almeida[6], Augusto Cézar Apolinário dos Santos[7], Jordana Alícia Silveira Lopes[8], Nathalia Noyma Sampaio Magalhães[9], Daniela O. W. Rodrigues[10]

ABSTRACT

Introduction: Vitamin D (VD) deficiency is frequent in sickle cell disease (SCD) due to chronic inflammatory status, kidney and endothelial damage, hyperhemolysis and melanoderma. Currently, the supplementation of this nutrient in sickle cell patients is important due to its systemic and immunological action. **Objectives:** To analyze the impact of VD in children with SCD. **Methods:** This is an integrative literature review, which analyzed studies, originally published in English and Portuguese, in the last ten years, in humans, using the MedLine, SciELO and LILACS databases as References. The search was performed by consulting the MeSH. The descriptors used were: "children"; "vitamin D"; "sickle cell anemia"; "supplementation". 32 articles were identified from the search phrase. When applying the inclusion criteria, nine articles were chosen for the study. **Results:** Among the included articles, six evaluated the prevalence of VD deficiency in children with sickle cell anemia, and the other three reported on VD supplementation in children with sickle cell anemia. All studies showed that children treated with VD replacement had a decrease in emergency room visits and greater hemodynamic stability during treatments. **CONCLUSION:** Further randomized controlled trials should be carried out to identify the role of VD in quality of life and in the reduction of sickle cell morbidity. The contribution of this paper is to recognize that there is evidence about vitamin D outside of randomized controlled trials.

Keywords: Child; Sickle cell anemia; Vitamin D.

[1] Medical student at Centro Universitário Presidente Antônio Carlos and scholarship at Fundação Hemominas/FAPEMIG. Juiz de Fora, Minas Gerais, Brazil.

[2] Nurse, PhD student in Public Health at Faculdade de Medicina da Universidade Federal de Juiz de Fora (UFJF). Juiz de Fora, Minas Gerais, Brazil.

[3] Medical student at Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (Suprema). Juiz de Fora, Minas Gerais, Brazil.

[4] Nutritionist, Master in Public Health at Universidade Federal de Juiz de Fora (UFJF). Juiz de Fora, Minas Gerais, Brazil.

[5] Phisician in Primary Care at Prefeitura Municipal de Juiz de Fora. Juiz de Fora, Minas Gerais, Brazil.

[6] Medical student at Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (Suprema). Juiz de Fora, Minas Gerais, Brazil.

[7] Medical student at Centro Universitário Presidente Antônio Carlos. Juiz de Fora, Minas Gerais, Brazil.

[8] Phisician in Primary Care at Prefeitura Municipal de Juiz de Fora. Juiz de Fora, Minas Gerais, Brazil.

[9] Medical student at Faculdade de Ciências Médicas e da Saúde de Juiz de Fora and scholarship at Fundação Hemominas/FAPEMIG. Juiz de Fora, Minas Gerais, Brazil.

[10] Hematologist at Fundação Hemominas Juiz de Fora, PhD in Brazilian Medicin at Universidade Federal de Juiz de Fora (UFJF). Juiz de Fora, Minas Gerais, Brazil.

RESUMO

Introdução: A deficiência de Vitamina D (VD) é frequente na doença falciforme (DF) em decorrência do *status* inflamatório crônico, danos renais, endoteliais, hiperhemólise e melanodermia. Atualmente, a suplementação desse nutriente em falcêmicos tem se mostrado importante devido sua ação sistêmica e imunológica. **Objetivos:** Analisar o impacto da VD em crianças com DF. **Métodos:** Trata-se de uma revisão integrativa da literatura, onde foram analisados estudos, publicados originalmente em inglês e português, dos últimos dez anos, em humanos, tendo como referência as bases de dados MEDLINE, SciELO e LILACS. A busca foi efetuada mediante a consulta ao MeSH. Os descritores utilizados foram: "*children*"; "*vitamin D*"; "*sickle cell anemia*"; "*supplementation*". Foram identificados 32 artigos a partir da frase de pesquisa. Ao aplicar os critérios de inclusão, nove artigos foram eleitos para o estudo. **Resultados:** A partir da análise dos artigos incluídos, 6 avaliaram a prevalência da deficiência de VD em crianças com anemia falciforme e os outros três artigos relataram sobre a suplementação de VD em crianças também com anemia falciforme. Todos os estudos mostraram que as crianças tratadas com reposição de VD tiveram uma diminuição de idas ao pronto-socorro e maior estabilidade hemodinâmica durante os tratamentos. **Conclusão:** Outros ensaios clínicos randomizados devem ser realizados para identificar o papel da DV na qualidade de vida e na redução da morbidade falciforme. A contribuição deste artigo é reconhecer que há evidências sobre a vitamina D fora dos ensaios clínicos randomizados.

Palavras-chaves: Criança; Anemia falciforme; Vitamina D.

Associate Editor Responsible:

Dra. Ana Paula Fernandes

Faculdade de Ciências Médica de Minas Gerais

Belo Horizonte/MG, Brazil

Institution where the word was carried out:

Fundação Hemominas, Juiz de Fora, Minas Gerais, Brazil.

Funding support:

Fundação Hemominas and FAPEMIG

Corresponding Author:

Daniela de Oliveira Werneck Rodrigues

Rua Doutor Antônio Carlos, 430/1400 - ZIP Code:36010-560

Juiz de Fora/MG, Brazil

E-mail: danielawerneckhemato@hotmail.com

Conflict of Interest:

None.

Received on: 10 October 2022

Approved on: 18 November 2022

Publication Date: March 27, 2023.

DOI: 10.5935/2238-3182.2023e33201

Introduction

Sickle cell disease (SCD) is caused by the presence of an abnormal hemoglobin called HbS, resulting from the substitution of glutamic acid for valine, in position number six of the beta-globulin chain[1]. It is the most common hereditary syndrome in the world and its main representatives are: sickle cell anemia (Hb SS), S beta-thalassemia and SCD SC and SD[2]. The clinical manifestations of SCD are closely related to HbS, which in a situation of absence or decrease in oxygen tension undergoes polymerization, acquiring sickle morphology. Consequently, these sickling erythrocytes cause, directly or indirectly, ischemia and chronic hemolysis, resulting in reduced quality of life for sickle cell patients. Sickling of red blood cells in hypoxia causes ischemia and infarction of target organs, such as brain, eyes, heart, lungs, kidneys, spleen and liver. The splenic alteration deserves to be highlighted in these patients since this functional asplenia and less opsonization of microorganisms, increasing the susceptibility to infection, especially by: *Streptococcus pneumoniae* and *Haemophilus influenzae*. Moreover, the pathophysiology of SCD involves a decrease in the bioavailability of nitric oxide, which has antioxidant, antithrombotic and anti-aggregating effects, in addition to being essential for the relaxation of the endothelial muscles[1,2].

According to the Brazilian Society of Endocrinology and Metabology, hypovitaminosis D is highly prevalent in the general population, with an incidence of up to 90% depending on the cohort studied, thus constituting a global public health problem[3]. In SCD, vitamin D (VD) is an important deficiency, resulting from a multifactorial process, mainly associated with increased catabolism and deficit in nutrient intake. The pathophysiology of hypovitaminosis D in these patients involves several factors, the main ones being: the reduction of VD absorption by reducing appetite and/or damage to the intestinal mucosa, the state of chronic hemolysis that demands a greater amount of nutrients, kidney damage which hinders the activation of this vitamin, melanoderma which reduces the production of VD by sunlight and chronic inflammation, which, in itself, already reduces the levels of this micronutrient[4].

The age group most prone to the development of hypovitaminosis D in people with SCD is the infant group, especially during episodes of sickle cell crisis: pain, acute chest syndrome and aplastic crisis[1,5]. It is believed that the lack of VD in this age group is related to reduced appetite, poor nutrients intake in nutrients, high frequency of infectious complications and socioeconomic conditions[1]. Thus, the exposure of individuals to such factors can alter the absorption and activation of the micronutrient, since the main source of VD is through endogenous cutaneous synthesis or food intake, such as salmon, eggs, mushrooms and cod[3].

Recent studies indicate that this vitamin is of fundamental importance in the body, since it acts in a systemic way, influencing bone metabolism, immunity, adipose tissue, cognition and cardiovascular, respiratory and renal systems[3]. It is suggested that adequate serum levels of VD can act positively on frequent complications of SCD by optimizing the individual's adaptive response through its systemic and immunological action, which indicates that supplementation of this vitamin or correction of hypovitaminosis D can exert beneficial effects in some complications, such as nephropathy, asthma, chronic pain and cardiovascular disorders, while its deficiency can exacerbate the clinical manifestations of SCD[4,6].

VD deficiency constitutes a challenge both for the person with SCD and for the attending physician, since the latter confuses the clinical manifestations of hypovitaminosis with pain crisis because bone and muscle pains can mimic the acute vaso-occlusive pain crisis or chronic pain syndrome[7,8]. Furthermore, bone disorders can be caused or at least exacerbated by a lack of VD[9].

Studies on the impact of VD supplementation in children with SCD are of fundamental importance to verify the reduction of morbidity and improvement in the quality of life of this population, considering the beneficial effect of this micronutrient. The present study aims to carry out an integrative review of the effect of VD in children with SCD.

Methods

This is an integrative literature review whose research object is the impact of vitamin D on children with Sickle Cell Disease. For this review, the ensuing methodological procedures were followed: 1) Formulation of the question and the objectives of the review; 2) Establishment of criteria for selecting articles; 3) Categorization of studies; 4) Evaluation of studies included in the integrative review; 5) Data analysis and presentation of results[9].

The benchmark survey was carried out during the period from September 2020 to March 2022, including studies from the last ten years. For the selection of articles, three electronic databases were used to expand the scope of the research, avoiding possible bias in this stage of the process of producing such an integrative review, being: Publisher Medline (PubMed), Scientific Electronic Library Online (SciELO) and Latin American and Caribbean Literature in Health Sciences (LILACS). For the search strategy, the following descriptors were used: "sickle cell anemia", "vitamin D", "Supplementation" and "children", which were combined using the AND operator. For the Pubmed search, the descriptors were identified in the Medical Subject Headings (Mesh), available from the US National Library of Medicine, and the search expression was used: ("Vitamin D" [MeSH Terms] AND "supplementation" [MeSH Terms]) AND "children" [MeSH Terms]) AND "sickle cell anemia" [MeSH Terms]. For search on Lilacs and SciELO, Health Sciences Descriptors (DeCS) were identified, and are available on the Virtual Health Library Portal.

In order to establish the adequacy of the literature found for this review study, the following inclusion criteria were established: a) articles with human beings; b) articles published in the last 10 years; c) patients of both sexes; d) pediatric child patients; e) articles published in English and Portuguese. The exclusion criteria were developed to eliminate articles that did not use the following parameters in their methodology: a) review studies; b) short communication; c) publications in other languages; and e) case reports.

The searches were carried out by three independent examiners, from September 2020 to March 2022. Disagreements during the selection and eligibility stages were resolved by consensus. Due to the nature of the research, it was not necessary to submit the project for approval by the Research Ethics Committee.

As seen in Figure 1, the search resulted in 78 articles related to the topic addressed, of which 46 were excluded due to duplicity in the consulted databases. After reading the abstracts, sixteen articles were excluded and nine were chosen for inclusion in this study.

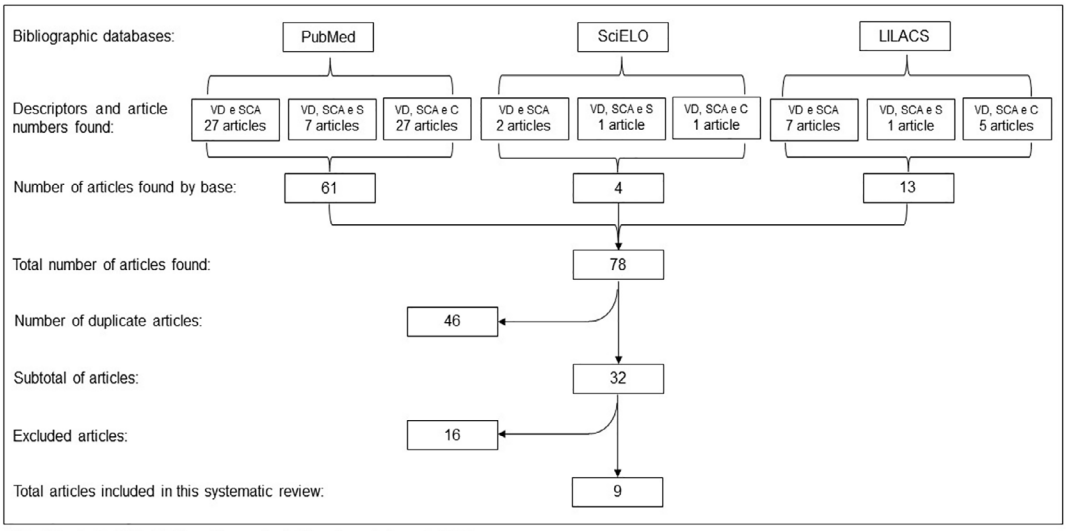

Figure 1. Flowchart of article selection.
Legend: VD = Vitamin D; SCA = Sickle cell anemia; S = Supplementation; C = Children.

Literature Review

From the analysis of the nine articles included in the present literature review, six evaluated the prevalence of vitamin D deficiency in children with sickle cell anemia and the other three articles reported on vitamin D supplementation in children also with sickle cell anemia. All studies showed that children treated with vitamin D replacement had a decrease in emergency room visits and greater hemodynamic stability during treatments. Table 1 presents the main findings of the literature review.

Table 1. Result of the literature review.

Author and year	Sample and Location	Methods	Objective
Wykes et al. (2014)[10]	81 children from King's College Hospital in England.	Cross-sectional study, to evaluate emergency care and hospitalization in 2006, analyzing whether Vitamin D deficiency is clinically significant in children with sickle cell anemia, observing the possible correction of deficiency with high doses of vitamin D in a short period of time.	Eleven children were treated on 15 different occasions with 300,000IU of ergocalciferol. The mean 25-OHD level increased from 6.1 to 27.9µg/L measured after about 33 days. All children initially had vitamin D deficiency and after treatment, six (40%) still had deficient levels, three (20%) were classified as insufficiency and six (40%) had sufficient vitamin D. Similarly, 28 different children were treated with high-dose oral cholecalciferol on 64 separate occasions. The mean dose was 5234IU/kg, with a range of 2105 to 9722. 25-OHD levels increased from an average of 11.3 to 45µg/L, measured after a median of 24 days. After treatment, 3 (4.6%) children still had deficient levels of 25-OHD, 6 (9.3%) had insufficiency, and 53 (83%) had sufficient vitamin D.
Dougherty et al. (2015)[11]	44 children aged 5 to 20 years (21 with SCDSS and 23 healthy) were recruited at Children's Hospital in the United States.	Controlled and randomized clinical trial to evaluate the safety and efficacy of two daily oral doses (4,000 vs. 7,000IU) of cholecalciferol (vit D3) over a 12-week period in children and young adults with sickle cell anemia and healthy controls, during the period from April 2012 to January 2013.	At baseline, 95% of Sickle Cell Anemia (SCA) subjects and 87% of controls had suboptimal vit D status (mean±SD, 19.2±7.2 and 22.3±9.3ng/ml, respectively). After 12 weeks of supplementation, both doses of D3 were safe and well tolerated. None of the groups met the a priori efficacy criterion of 25 (OH) D ≥32ng/ml in >80% of subjects (45% in SCD-SS and 63% in controls). However, for both SCA and healthy subjects, the deficient state (<20ng/ml) of vitD was eliminated only in those who received 7,000 IU/d. For subjects with SCD-SS, at 12 weeks, there was a significant increase (p<0.05) in fetal hemoglobin and reduction in platelet counts (79% at baseline vs. 66% at 12 weeks). There was a trend (p=0.08) of increased fetal hemoglobin in those who received 7000 IU/d but not 4000IU/d vit D3.
Martyres et al. (2016)[12]	91 children and adolescents aged 2 to 18 years from Children's Hospital of Eastern Canada.	Retrospective study to analyze pediatric outpatients between March 2012 and November 2013, through serum levels of vitamin D, zinc, B6, B12, folate and homocysteine in children with sickle cell anemia to provide a clinical picture of the nutritional status of patients and thus test the association between nutrient levels and disease severity indicators.	Almost half of the sample (42%) had multiple nutrient deficiencies and 27% had a single insufficiency or deficiency. The most common deficiency insufficiency was zinc at 57%, followed by calcidiol (25 OHD) (52%). It was observed that 16% of the patients had low levels of vitamin B6, while the levels of folate, calcitriol (1.25 (OHD) and homocysteine were normal. An increase in the number of vitamin deficiencies was associated with an increase in the severity of the disease (p=0.018) Zinc deficiency was significantly associated with a greater number of pain attacks at home (p=0.001) and an increased incidence of hospitalizations.

Author and year	Sample and Location	Methods	Objective
Adegoke et al. (2017)[13]	90 children (steady-state disease) and 75 children (healthy controls) from Nigeria.	Cross-sectional study to evaluate the effects of three months of vitamin D supplementation on the cytokines of children with sickle cell anemia, through medical records during the year 2017.	It was observed that IL-2, 6, 8, 12, 17 and 18 were higher in children with SCA than in controls ($p \leq 0.001$), but without significant variation in IL-11 and 13 ($p=0.131$ and 0.057, respectively). Patients with suboptimal serum 25-OHD had higher IL-6, 8, and 18 ($p=0.003$, 0.010, and 0.002, respectively) and lower IL-11 levels ($p=0.005$). Significant positive effects of treatment were observed: post-supplementation, serum 25-OHD increased by 23.3ng/mL, $p<0.001$; pro-inflammatory cytokines IL-2, 6, 8, 17 and 18 ($p<0.001$) were reduced and anti-inflammatory cytokines IL-11 increased, $p<0.001$.
AlJama et al. (2018)[14]	640 patients aged 12 years and over, from the Qatif Central Hospital in Saudi Arabia.	Cross-sectional study to estimate the level of 25-hydroxyvitamin D [25(OH) D] and the frequency of 25(OH) D deficiency among patients with Sickle Cell Anemia by age group and disease status, through a screening during the period 1 of January 2010 to December 31, 2014.	Women with Sickle Cell Anemia (SCA) had slightly higher mean levels of 25(OH) D compared to men, however, the difference was not statistically significant ($p=0.106$). Patients with SCA without crisis constituted the majority of the total study population (n = 493, 73.6%) and of the evaluable population. For the entire population, the mean 25(OH)D level was statistically significantly higher in patients with SCA with crisis (10.1 [8.6]ng/mL) versus patients with SCA without crisis (15.7 [18.2]ng/mL) ($p<0.001$). Most of the evaluated patients (82%) had suboptimal 25(OH)D, 67% of these were also vitamin D deficient (<20ng/mL). Steady-state (non-crisis) patients had higher levels of 25(OH)D, especially the elderly (>65 years) and the difference between age groups was statistically significant ($p<0.001$).
Kaitlyn et al. (2018)[15]	45 children and adolescents aged 2 to 19 years attended at BC Children's Hospital, Canada.	Retrospective review to evaluate serum concentrations of 25-hydroxyvitamin D (25OHD) and estimate the prevalence of deficiency in children and adolescents with sickle cell anemia, by reviewing medical records of patients with sickle cell anemia from 2012 to 2017.	The mean concentration ± SD 25OHD was 79.1±35.9nmol/L; the prevalence of vitamin D deficiency (<40nmol/L) and insufficiency (<75nmol/L) was 17% and 50%, respectively. Season, hemoglobin concentration, and ALP activity were significantly associated with serum 25OHD concentrations in children and adolescents with SCD, after adjusting for confounders and repeated measures of subjects. Mean 25OHD concentrations evaluated during the months of July to September were significantly higher (28 (95% CI: 16-40) nmol/L higher, $p<0.001$) compared to January to March. A 1g/L increase in hemoglobin concentration was associated with a 0.4 (95% CI: 0.1; 0.8) nmol/L increase in mean serum 25OHD concentration ($p=0.01$). A 1U/L increase in ALP activity was associated with a 0.1 (95% CI: 0.1, 0.2) nmol/L increase in mean serum 25OHD concentration ($p=0.03$).

Author and year	Sample and Location	Methods	Objective
Mandese et al. (2019)[16]	52 children and adolescents (38 with HbSS and 14 with HbSC), aged between 3 and 18 years from Italy.	Cross-sectional study to assess the growth pattern, endocrine complications, metabolic changes and detect the relationship between these conditions and the severity of sickle cell anemia in children and adolescents affected by sickle cell disease between January and June 2017.	The prevalence of metabolic alterations and endocrine complications was high: 48 of 52 patients had at least one metabolic and/or endocrine alteration. Of the patients, 41 (79%), 6 (11.5%) and 1 (1.9%) presented, respectively, one, two and three alterations at the same time. The most detected conditions were vitamin D insufficiency (84.7%), insulin resistance (11.5%) and, to a lesser extent, GHD (3.8%). In particular, in 63.5% of patient's vitamin D levels were between 10 and 30 ng/ml, while in 21.2% they were <10ng/ml. A significant negative relationship was demonstrated between plasma vitamin D levels and the clinical severity of the disease, represented by the number of hospitalizations (R=-0.29, p=0.040), mean number of hospitalization days (R=- 0.29, p=0.034) and mean number of hospital admissions in the last 5 years (R=- 0.36, p=0.009).
Hood et al. (2020)[17]	110 children aged 8 to 16 from the United States.	Retrospective review to identify the prevalence of vitamin D deficiency and explore the relationship between vitamin D supplementation and emergency room visits in pediatric patients with sickle cell anemia, by analyzing medical records during the 6-year study period.	It was observed that 45% of patients were vitamin D deficient and only 20% had sufficient levels of vitamin D. This number increased to 55% when we examined only patients who did not receive vitamin D supplementation. For patients supplemented with vitamin D, the number of emergency room visits was significantly lower after they reached the sufficient range (≥30ng/mL), p=0.03.
Grégoire-Pelchat et al. (2021)[18]	38 patients aged 5 to 17 years with Sickle Cell Disease from Canada.	Randomized controlled trial to assess the effectiveness of supplementation to raise 25(OH)D to sufficient levels (25(OH)D ≥ 75 nmol/l) and the safety of the intervention, by collecting exploratory data on the clinical impact of the vitamin D bolus.	Bolus administration of vitamin D caused a greater increase in 25(OH)D levels compared with placebo administration (20±16 nmol/l vs. 2±19nmol/l; p=0.003) and better correction of micronutrient deficiency. Administration of a high-dose bolus of vitamin D combined with 1,000 IU of vitamin D3 daily was more effective in raising 25(OH)D levels compared to daily supplementation alone in children with sickle cell disease. Hypercalcemia and hypercalciuria were not observed in children with sickle cell disease. During the study, however, a significant number of children in the bolus group had gastrointestinal symptoms in the first month (p=0.04). However, they did not observe differences for other outcomes between the groups.

Source: Elaborate by Authors (2022).

Discussion

Vitamin D deficiency is a pandemic health problem, including in areas with high exposure to sunlight. Evidence from different areas have documented that vitamin D deficiency is common in children and adults with SCD[19]. Usually, patients with FD are melanodermic, which indicates greater amount of melanin - pigment produced by melanocytes that act as a skin barrier against sunlight, thus individuals with darker skin tones need more sun exposure to achieve considerable vitamin D production[20].

As the majority of vitamin D in humans results from sun exposure, the incidence of deficiency would be expected when considering latitude, season and skin pigmentation. However, it must also be considered that the prevalence of this deficiency varies according to sex, life stages and food intake[21].

Vitamin D metabolism is complex due to the involvement of different organs, including skin, intestines, liver, kidney and parathyroid[22]. Patients with SCD have some peculiar characteristics that can lead to the development of vitamin D deficiency, such as decreased appetite or reduced nutrient absorption due to damage to the intestinal mucosa. The continuous production of red blood cells to compensate for the anemia characteristic of SCD causes an increase in the basal metabolic rate with greater nutritional demands[23,24]. Furthermore, in patients with SCD and renal failure, the conversion of vitamin D to its active form may be reduced. Finally, vitamin D binding protein levels can be low[25]. The importance of assessing vitamin D in patients with SCD is supported by the demonstration that the deficiency is more frequent among children with SCD than in controls[19].

Nine articles published between 2014 and 2021 were included in this review. Such research was carried out in the following locations: London, the United States, Italy, Canada, Nigeria and Saudi Arabia, with methodological designs in the formats of a cross-sectional study, retrospective review and clinical trial. The analyzed studies were developed with children and adolescents aged between 5 and 20 years. The largest sample was found in the study carried out in Saudi Arabia with 640 participants, while the smallest was observed in the study carried out in Canada, with 38 children and adolescents.

In general, the studies used in their methodology the evaluation of medical records, application of questionnaires, dosage of cytokines, assessment of serum levels of vitamins and minerals, administration of vitamin D supplementation and blood measurements. In all studies, insufficient levels of vitamin D were found among the participants.

Özen et al. (2013)[26] reported that 50% of the examined population has endocrine disorders mainly characterized by vitamin D insufficiency or deficiency. This micronutrient exerts systemic effects of fundamental importance, being closely related to the proper development of bones in childhood, with the regulation of calcium, glucose and lipid metabolism and cardiovascular function[27]. Furthermore, vitamin D is believed to influence peripheral and parasympathetic nerve function through anti-inflammatory effects mediated by reduced pro-inflammatory cytokines, prostaglandin release, and effects on T25 cell responses. Thus, vitamin D deficiency can lead to changes in neural and immune processes.

Currently, vitamin D supplementation has been considered a potential target to reduce pain in sickle cell patients, as they are often affected by painful crises. Pain is the most common cause of emergency room visits, which profoundly affects quality of life. Unfortunately, there is currently no uniform classification in the literature; however, serum levels of 25-hydroxyvitamin D (25-OHD) of ≤20ng/mL are generally considered to be deficient[28]. It has been suggested that vitamin D supplementation at a high loading dose combined with daily use of 1,000IU of vitamin D3 is more efficient in raising VD levels compared to daily supplementation alone[18].

In general, the articles found that vitamin D supplementation promoted positive effects on children's health, including reducing hospitalization episodes and disease severity, thus being important to improve quality of life. The article by Adegoke et al (2017)[13] found that vitamin D supplementation increased serum anti-inflammatory cytokines and decreased pro-inflammatory cytokines in children with sickle cell disease. Recent interventional studies have shown promising effects of vitamin D supplementation on cancer pain and muscular pain - but only in patients with insufficient levels of vitamin D when starting the intervention. Possible mechanisms for vitamin D in pain management are the anti-inflammatory effects mediated by reduced cytokine and prostaglandin release and effects on T-cell responses. The recent finding of vitamin D-mediated inhibition of prostaglandin E2 (PGE2) is especially interesting and exhibits a credible mechanistic explanation[19].

As evidenced in the studies, there was a high prevalence of vitamin insufficiencies or deficiencies in children with SCD, which were associated with increased disease severity. The precise mechanisms by which vitamin D supplementation reduces the rate of pain-related emergency room visits remain unclear; however, it is known that vitamin D deficiency can worsen the disease process and increase the risk of complications by altering the neural and immunological processes that contribute to the experience of pain[19].

It is known that the survival of children with sickle cell disease has increased, especially in recent decades, due to early diagnosis and better quality of care. However, the incidence of long-term complications, such as metabolic and endocrine disorders, has been very high[28]. In this regard, nutritional deficiencies or insufficiencies are commonly observed, specifically, the literature shows that children with SCD are at risk of vitamin D, B6 and zinc deficiency[21,29] as well as vitamin B12 and folate deficiency; in addition to high serum levels of homocysteine[30,31].

It is necessary to consider some factors that can be limiting in the execution of the studies, such as: the sample size that affected the ability to detect significant effects, the different formulations of vitamin D supplements available, the unpleasant taste, the limited adherence or the inability to determine adherence, conducting non-randomly controlled studies, and possible confounders.

Given the lack of high-quality controlled studies, it is necessary to encourage research in this area to better investigate the effect of vitamin D supplementation in individuals with SCD and guide clinical management.

Conclusion

From the analysis of the present integrative review, it was observed that sufficient serum levels of VD contributed to a reduction in the number of visits to the emergency room, a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory drugs, an increase in fetal hemoglobin and a decline in metabolic complications. Although other studies are necessary to identify the specific mechanisms as well as the relationship between VD and PD, reviews are extremely relevant to the scientific community, as they direct and influence new research whose results can contribute to quality of life and reduction of morbidity in children with SCD.

In conclusion, VD plays a fundamental systemic role in sickle cell patients, enabling health, well-being and quality of life broadly. The contribution of this paper is to recognize that there is evidence about vitamin D outside of randomized controlled trials.

Authors contribution

Conceptualization, Investigation, Methodology, Visualization & Writing – Review & Editing: Rodrigues DOW, Motta FVR, Neto AAR, Santos OF, Espósito TS. Project administration, Supervision & Writing – Original Draft: Magalhães NNS, Gusmão AC, Santos ACA, Lopes JAS, Almeida RDM.

Copyright

References

1. Oliveira JF, Vicente NG, Santos JPP, Weffort VRS. Vitamin D in children and adolescents with sickle cell disease: an integrative review. Rev Paul Pediatr. 2015 Jul/Sep;33(3):349-54.
2. Jesus JA. Doença falciforme: condutas básicas para o tratamento. Brasília (BR): Ministério da Saúde; 2012.
3. Maeda SS, Borba VZC, Camargo MBR, Silva DMW, Borges JLC, Bandeira F, et al. Recomendações da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) para o diagnóstico e tratamento da hipovitaminose D. Arq Bras Endocrinol Metab. 2014;58(5):411-33.
4. Soe HHK, Abas AB, Than NN, Ni H, Singh J, Said ARBM, et al. Vitamin D supplementation for sickle cell disease. Cochrane Database Syst Rev. 2020;5(5):CD010858. DOI: https://doi.org/10.1002/14651858.CD010858.pub3
5. AlJama Ali, AlKhalifah M, Al-Dabbous IA, Alqudaihi G. Vitamin D deficiency in sickle cell disease patients in the Eastern Province of Saudi Arabia. Ann Saudi Med. 2018 Mar/Apr;38(2):130-6.
6. Nolan VG, Nottage KA, Cole EW, Hankins JS, Gurney JG. Prevalence of vitamin D deficiency in sickle cell disease: a systematic review. PLos One. 2015 Mar;10(3):e0119908.
7. Arlet JB, Courbebaisse M, Chatellier G, Eladari D, Souberbielle JC, Friedlander G, et al. Relationship between vitamin D deficiency and bone fragility in sickle cell disease: a cohort study of 56 adults. Bone. 2013 Jan;52(1):206-11.
8. Chapelon E, Garabedian M, Brousse V, Souberbielle JC, Bresson JL, Montalembert M. Osteopenia and vitamin D deficiency in children with sickle cell disease. Eur J Haematol. 2009 Dec;83(6):572-8.
9. Rother ET. Revisão sistemática x revisão narrativa. Acta Paul Enferm. 2007;20(2):vi.
10. Wykes C, Arasaretnam A, O'Driscoll S, Farnham L, Moniz C, Rees DC. Vitamin D deficiency and its correction in children with sickle cell anaemia. Ann Hematol. 2014 Dec;93(12):2051-6.
11. Dougherty KA, Bertolaso C, Schall JI, Smith-Whitley K, Stallings VA. Safety and efficacy of high-dose daily vitamin D3 supplementation in children and young adults with sickle cell disease. J Pediatr Hematol Oncol. 2015 Jul;37(5):e308-e15.
12. Martyres DJ, Vijenthira A, Barrowman N, Harris-Janz S, Chretien C, Klaassen RJ. Nutrient insufficiencies/deficiencies in children with sickle cell disease and its association with increased disease severity. Pediatr Blood Cancer. 2016 Jun;63(6):1060-4.
13. Adegoke AS, Smith COS, Adekiled AD, Figueiredo MS. Relationship between serum 25-hydroxyvitamin D and inflammatory cytokines in paediatric sickle cell disease. Cytokine. 2017 Apr;96:87-93.
14. AlJama A, AlKhalifah M, Al-Dabbous IA, Alqudaihi G. Vitamin D deficiency in sickle cell disease patients in the Eastern Province of Saudi Arabia. Ann Saudi Med. 2018 Mar;38(2):130-6.
15. Samson KLI, McCartney H, Vercauteren SM, Wu JK, Karakochuk CD. Prevalence of vitamin D deficiency varies widely by season in Canadian children and adolescents with sickle cell disease. J Clin Med. 2018;7(2):14.
16. Mandese V, Bigi E, Bruzzi P, Palazzi G, Predieri B, Lucaccioni L, et al. Endocrine and metabolic complications in children and adolescents with sickle cell disease: an Italian cohort study. BMC Pediatr. 2019 Feb;19(1):56.
17. Hood AM, Quinn CT, King CD, Shook LM, Peugh JL, Crosby LE. Vitamin D supplementation and pain-related emergency department visits in children with sickle cell disease. Complement Ther Med. 2020;49:102342.
18. Grégoire-Pelchat P, Pastore Y, Robitaille N, LeMay S, Khamessan A, Kleiber N, et al. Comparison of two vitamin D supplementation strategies in children with sickle cell disease: a randomized controlled trial. Br J Haematol. 2021 Jan;192(2):385-94.
19. Nolan VG, Nottage KA, Cole EW, Hankins JS, Gurney JG. Prevalence of vitamin D deficiency in sickle cell disease: a systematic review. PLoS One. 2015 Mar;10(3):e0119908.
20. Rovner AJ, Stallings VA, Kawchak DA, Schall JI, Ohene-Frempong K, Zemel BS. High risk of vitamin D deficiency in children with sickle cell disease. J Am Diet Assoc. 2008 Sep;108(9):1512-6.

21. Buison AM, Kawchak DA, Schall J, Ohene-Frempong K, Stallings VA, Zemel BS. Low vitamin D status in children with sickle cell disease. J Pediatr. 2004 Nov;145(5):622-7.

22. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010 Dec;376(9757):2018-31.

23. Barden EM, Kawchak DA, Ohene-Frempong K, Stallings VA, Zemel BS. Body composition in children with sickle cell disease. Am J Clin Nutr. 2002 Jul;76(1):218-25.

24. Singhal A, Parker S, Linsell L, Serjeant G. Energy intake and resting metabolic rate in preschool Jamaican children with homozygous sickle cell disease. Am J Clin Nutr. 2002 Jun;75(6):1093-7.

25. Helde-Frankling M, Björkhem-Bergman L. Vitamin D in pain management. Int J Mol Sci. 2017 Oct;18(10):2170.

26. Özen S, Ünal S, Erçetin N, Taşdelen B. Frequency and risk factors of endocrine complications in Turkish children and adolescents with sickle cell anemia. Turk J Hematol. 2013 Mar;30(1):25-31.

27. Lee MT, Licursi M, McMahon DJ. Vitamin D deficiency and acute vaso-occlusive complications in children with sickle cell disease. Pediatr Blood Cancer. 2015 Apr;62(4):643-7.

28. Nolan VG, Nottage KA, Cole EW, Hankins JS, Gurney JG. Prevalence of vitamin D deficiency in sickle cell disease: a systematic review. PLoS One. 2015;10(3):e0119908.

29. Prasad AS. Zinc deficiency in patients with sickle cell disease. Am J Clin Nutr. 2002 Feb;75(2):181-2.

30. Al-Momen AK. Diminished vitamin B12 levels in patients with severe sickle cell disease. J Intern Med. 1995 Jun;237(6):551-5.

31. Kennedy TS, Fung EB, Kawchak DA, Zemel BS, Ohene-Frempong K, Stallings VA. Red blood cell folate and serum vitamin B12 status in children with sickle cell disease. J Pediatr Hematol Oncol. 2001 Mar;23(3):165-9.