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# Updates on Prevalence of Vitamin D Deficiency and the Associated Outcomes in Sickle Cell Disease Patients: A Systematic Review

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**Abstract**
**Objectives:** To evaluate and synthesize the latest evidence on the prevalence of vitamin D deficiency (VDD) in patients with sickle cell disease (SCD).**Methods:** A total of 866 pertinent publications were found after a comprehensive search across four databases. 53 full-text publications were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; eight studies finally satisfied the requirements for inclusion. **Results:**We included eight cross-sectional studies with a total of 1961 SCD patients, of whom 674 (34.4%) were males. There is a variation in VDD prevalence, which ranged from 7.6% to 67%, with an overall prevalence of 48.5%. Alarmingly high rates were observed in certain regions, particularly among children. Key findings suggest that VDD in SCD patients is linked to low dietary intake, inadequate supplementation, and poor cutaneous synthesis of vitamin D. While some studies did not identify direct short-term correlations between vitamin D levels and SCD complications, others reported better hematological profiles with sufficient vitamin D. VDD is associated with increased risks of bone health issues, recurrent infections, vaso-occlusive crises, acute pain episodes, anemia, and the need for blood transfusions. **Conclusion:**This review shows a high prevalence of VDD among SCD patients, though it varies across regions and demographics. While the link between VDD and complications of SCD is inconsistent, there is a relationship between adequate vitamin D levels and improved clinical outcomes. The findings underscore the importance of routine screening, dietary supplementation, and tailored interventions. Longitudinal studies are needed in the future to clarify causality and to inform evidence-based guidelines for managing VDD in SCD patients.
**Keywords;** Sickle cell disease; Vitamin D deficiency; Patient outcomes; Systematic review.

## Introduction

Normal bone development and maintenance in both adult and pediatric populations, as well as the control of inflammatory reactions and immune system activities, depend on vitamin D [1,2]. Because it causes negative clinical symptoms, VDD has recently gained attention in the field of public health [1]. A number of other medical conditions, including cardiovascular illnesses, asthma, infectious infections, muscle weakness, diabetes mellitus, autoimmune thyroid diseases, and various cancers, are linked to VDD in addition to rickets and bone problems [1–4].

One of the most prevalent hereditary diseases in the world is SCD [5]. Although the HbS allele is present in all of the genotypes that cause SCD, the most prevalent form is homozygous inheritance of the mutated beta S-globin chains (HbSS), which refers to conditions where sickle hemoglobin is produced. This results in a series of pathophysiological effects, such as hemolysis, oxidative stress, inflammation, infarction, and hypercoagulability [5-7]. Acute cerebrovascular accidents, painful crises, acute chest syndrome, sequestration crisis, aplastic crisis, and chronic hemolytic anemia are among the several clinical manifestations linked to SCD [5–9].

VDD has been recognized as one of the major public health concerns, especially in populations with chronic diseases. Among these populations, individuals with SCD are at a higher risk for several factors that include altered metabolism, reduced sun exposure, and complications related to chronic hemolysis. Vitamin D is an important nutrient for bone health, immune function, and overall health; thus, its deficiency is a concern in SCD patients who already have skeletal abnormalities, chronic pain, and increased susceptibility to infections. Although the prevalence

of VDD is increasingly recognized in the general population, there is still limited synthesized evidence regarding its prevalence among SCD patients. This gap calls for a systematic review that can collate recent data and provide insights into the burden and implications of this deficiency in this vulnerable group. Such evidence is required to guide targeted interventions and optimize clinical management strategies. The objective of this systematic review is to evaluate and synthesize the latest evidence on the prevalence of VDD in patients with SCD.

## Methods

### Search strategy

The systematic review was conducted in accordance with the PRISMA and GATHER criteria. A thorough search was conducted to find relevant studies on the prevalence of VDD in patients with SCD. The reviewers searched SCOPUS, Web of Science, Cochrane, and PubMed, four electronic databases, studies published within the last 10 years (2014-2024) were included. After removing any duplicates, we uploaded to Rayyan every abstract and title we could locate using electronic searches. The study texts that satisfied the inclusion criteria based on the abstract or title were then collected for a comprehensive analysis. The appropriateness of the extracted publications was evaluated independently by two reviewers, who also reviewed any inconsistencies.

### Study population—selection

The PEO (Population, Exposure, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Patients with SCD, (ii) Exposure: Testing vitamin D status, (iii)Outcomes: Prevalence of VDD.

### Data extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Participants' number, (v) Age, (vi) Gender, (vii)Population type, (viii) VDD cut-off point, (ix) Prevalence of VDD, (x) Main outcomes.

### Quality review

Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool can be used for cohort designs where individuals exposed to different staffing levels are tracked over time and is designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [10].

## Results

The specified search strategy yielded 866 publications **(Figure 1).** After removing duplicates (n = 424), 442 trials were evaluated based on title and abstract. Of these, 389 failed to satisfy eligibility criteria, leaving just 53 full-text articles for comprehensive review. A total of 8 satisfied the requirements for eligibility with evidence synthesis for analysis.

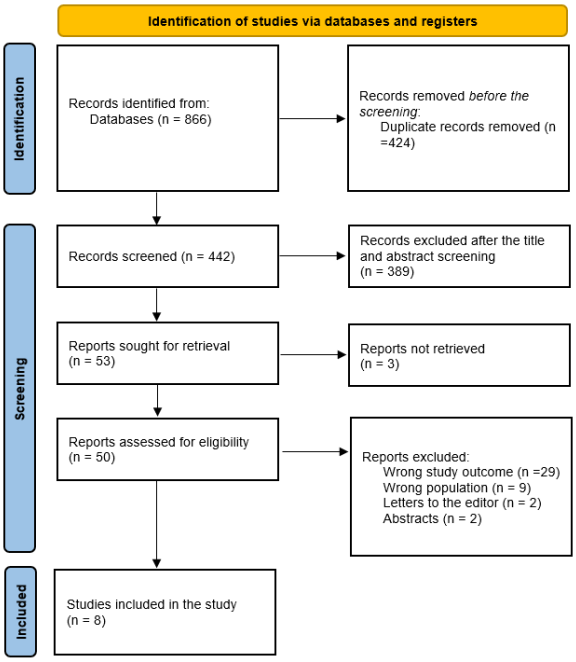


**Figure (1): PRISMA flowchart [11].**

**Sociodemographic and clinical outcomes**

We included eight studies with a total of 1961SCD patients,and 674 (34.4%) were males. Regarding study designs,all of the included studies were cross-sectionals [12-19]. Threestudies were implemented in Saudi Arabia [13, 14, 16], one in Canada[12], one in Nigeria[15], one in the USA [17], one in Egypt [18], and one in Kuwait [19].

The prevalence of VDD in SCD patients ranged from 7.6% [12] to 67% [13], with a total prevalence of 952 (48.5%).Geographically, there is a great variation in the prevalence rates of VDD, with alarmingly high rates being reported in some regions, especially among children. This calls for routine vitamin D screening and targeted interventions according to the unique needs of SCD patients.The main results of reviewed articles point out the high prevalence of VDD among SCD patients in different populations and age groups. A common finding from several studies is that VDD is related to low dietary intakes, insufficient dietary supplementation, and poor cutaneous synthesis of vitamin D. Some studies did not find a direct correlation between vitamin D level and SCD complications over short periods [12, 13], while others suggest that sufficient levels of vitamin D are associated with better hematological profiles [14, 15].

The common call from the studies reviewed is that VDD in SCD patients largely goes unnoticed despite having clinical consequences. Deficiency is associated with increased risks of bone health issues, including fractures and osteonecrosis, as well as increased susceptibility to recurrent infections and vaso-occlusive crises [18]. There is also a relationship between lower vitamin D levels and increased frequency of acute pain episodes, anemia, and blood transfusions. These findings underline the role of vitamin D as a potential modifiable risk factor in SCD management [17, 19].

**Table (1): Outcome measures of the included studies**

| Study ID | Study design | Country | Sociodemographic | Population type | VDD cut-off (nmol/L) | Prevalence of VDD | Main outcomes |
|---|---|---|---|---|---|---|---|
| **Grégoire-Pelchat et al., 2018 [12]** | Cross-sectional | Canada | N: 119<br>Mean age: 11.8<br>Males: 56 47(%) | Children | < 30 | 9 (7.6%) | There isa significant prevalence of VDD, which was linked to inadequate dietary and supplementary consumption as well as reduced cutaneous synthesis of vitamin D. Although vitamin D level was not linked to SCD problems during the previous two years, vitamin D sufficiency was linked to a better hematological profile. |
| **AlJama et al., 2018 [13]** | Cross-sectional | Saudi Arabia | N: 640<br>Age range: 12 to >65<br>Males: 241 (37.3%) | Both adults and children | <20 | 429 (67%) | Because of clinical presentation overlaps, vitamin D hypovitaminosis in SCD may not be getting enough attention. This health issue has significant clinical ramifications. |
| **Khan et al., 2024 [14]** | Cross-sectional | Saudi Arabia | N: 40<br>Mean age: 5-16<br>Males: 19 (47.5%) | Children | <20 | 32 (80%) | Due to its numerous health consequences, the incidence of VDD in children with SCD has drawn attention from all over the world. This study again demonstrated the deficiency status in virtually all SCD youngsters, which reiterates the need for robust governmental vitamin D screening and counseling programs. |
| **Ochogwu et al., 2021 [15]** | Cross-sectional | Nigeria | N: 153<br>Age range: 18-60<br>Males: 63 (42%) | Adults | <20 | 60 (39.2%) | Adults with SCA are more likely to have VDD, and those with lower vitamin D levels are more likely to be anemic and may need more blood transfusions. |
| **Tammas et al., 2024 [16]** | Cross-sectional | Saudi Arabia | N: 711<br>Age range: 3-56<br>Males: 137 (45.5%) | Both adults and children | <20 | 301 (42.3%) | In patients with SCD, VDD is a separate risk factor for the development of AVN. |
| **Lee et al., 2015 [17]** | Cross-sectional | USA | N: 95<br>Mean age: 10.6<br>Males: 48 (51%) | Children | <20 | 56 (58.9%) | The high incidence of VDD and its possible link to severe pain in SCD. |
| **Hamdy et al., 2018 [18]** | Cross-sectional | Egypt | N: 80<br>Mean age: 8.3<br>Males: 47 (58.8%) | Children | <20 | 51 (63.8%) | The Deficient group had a considerably greater history of bone fractures and recurring infections, as well as a higher incidence of hospitalization, vaso-occlusive crisis, and blood transfusions during the previous year. These results imply that VDD might be involved in the pathophysiology of hemolysis and other SCD complications. |
| **Adegoke et al., 2017 [19]** | Cross-sectional | Kuwait | N: 123<br>Mean age: 7.7<br>Males: 63 (51.2%) | Children | <20 | 14 (11.4%) | It is likely that a higher frequency of acute pain episodes is linked to lower serum vitamin D levels. |

**Table (2): Risk of bias assessment using ROBINS-I.**

| Study ID | Bias due to confounding | Bias in the selection of participants into | Bias in the classification of interventions | Bias due to deviations from the intended interval | Bias due to missing data | Bias in the measurement of outcomes | Bias in the selection of reported result | Overall bias |
|---|---|---|---|---|---|---|---|---|
| **Grégoire-Pelchat et al., 2018 [12]** | Low | Mod | Low | Low | Low | Mod | Low | Low |
| **AlJama et al., 2018 [13]** | Low | Mod | Low | Low | Low | Mod | Low | Low |
| **Khan et al., 2024 [14]** | Mod | Mod | Low | Low | Low | Low | Low | Low |
| **Ochogwu et al., 2021 [15]** | Mod | Mod | Low | Low | Low | Mod | Mod | Moderate |
| **Tammas et al., 2024 [16]** | Mod | Mod | Mod | Low | Low | Mod | Mod | Moderate |
| **Lee et al., 2015 [17]** | Mod | Mod | Low | Mod | Low | Mod | Mod | Moderate |
| **Hamdy et al., 2018 [18]** | Mod | Mod | Low | Low | Low | Mod | Mod | Moderate |
| **Adegoke et al., 2017 [19]** | Mod | Mod | Low | Low | Mod | Mod | Mod | Moderate |

**Discussion**

The findings of this review underscore the high prevalence of VDD among SCD patients, with notable geographical and demographic variations. Prevalence rates ranged from 7.6% to 67%, with an overall prevalence of 48.5%, indicating a significant burden of VDD in this population. This was lower than**Nolan *et al.*** who reported that the prevalence estimates in SCD communities vary from 56.4% to 96.4%, with a deficit defined as vitamin D <20ng/mL. However, the prevalence of VDD in the broader African American community seemed to be comparable to findings from the population-based National Health and Nutrition Examination Survey. Compared to Caucasians, the number of African American patients with and without SCD was much higher [20]. This was also lower than **Mohamed *et al.*** who found a 63.8% prevalence of VDD in SCD patients [21].

We demonstrated that etiologies for VDD are multifactorial; however, contributing factors include low dietary intake, low supplementation rates, and reduced cutaneous synthesis of vitamin D because of low sun exposure. Disproportionately affected were children, and early intervention is important. Although several studies found no short-term association of vitamin D with complications in SCD patients, there were other findings to the effect that adequate vitamin D is associated with superior hematologic profiles and therefore superior clinical outcomes. Similarly, **Nolan *et al.*** found that Vitamin D insufficiency is very common in both adult and pediatric SCD patients. Furthermore, a number of clinical trials comparing SCD patients to either healthy controls or non-SCD patients revealed that VDD is significantly more common in SCD patients [20].

The high incidence and elevated risk of VDD in SCD patients may be explained by a number of unusual features of the disease, including: decreased vitamin D binding protein levels because of the inflammatory state of SCD; elevated physiological demands because of the rapid turnover in the erythrocytosis process in SCD; and reduced levels of nutritional status, physical activity, and exercise in SCD patients [22-24].

The clinical implications of this review are far-reaching. Routine screening for vitamin D levels should be incorporated into the standard care for SCD patients, particularly for children and patients in regions with high deficiency prevalence. This will allow for early identification and intervention to prevent complications associated with VDD. Nutritional counseling and vitamin D supplementation should be emphasized to address dietary insufficiencies and ensure adequate intake. Management plans will also need to consider the various population needs based on geography and demographics. The prevention of VDD can potentially decrease not only the frequency of bone pain but also overall frequency of pain crises, anemia, and hospitalization, with resultant overall reduction in disease burden and improved quality of life for SCD patients.

**Strengths**

The strengths of this review include the fact that it was quite comprehensive in scope and included studies from geographically diverse regions, thereby offering a wide perspective on the prevalence of VDD among SCD patients. Both pediatric and adult populations are considered, which is crucial in age-specific trends and vulnerabilities. Moreover, the findings are clinically relevant, providing actionable insights directly applicable to the management of SCD patients.

**Limitations**

However, this review is not without its limitations. All the included studies were cross-sectional, which limits the ability to draw causal inferences about the relationship between VDD and SCD complications. Additionally, while the studies covered multiple countries, the geographical representation may not fully reflect regions with limited research on SCD or VDD prevalence. There is heterogeneity regarding the populations under study, the cut-off value considered for VDD, and differences in methodologies that may impair the comparability of such results. Finally, all the included studies are cross-sectional; therefore, one cannot delineate how correction of VDD would affect long-term outcomes in SCD patients, thus limiting the generalisability of recommendations.

**Conclusion**

This systematic review, therefore, points out a high prevalence of VDD among SCD patients with significant geographical and demographic variation. Though the relationship of VDD with complications of SCD is not consistently observed, evidence exists that adequate levels of vitamin D are associated with better hematological and clinical profiles. These findings emphasize the need for regular screening, dietary supplementation, and management strategies that are tailored to alleviate VDD in SCD patients. Longitudinal studies will be important in the future in establishing causality and the long-term impact of the correction of vitamin D levels on disease outcomes with a view to giving strength to clinical guidelines through evidence-based practice.

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