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Original

Defining vitamin D deficiency in patients with sickle cell disease; A meta-analysis

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Abstract

Introduction: Sickle cell disease (SCD) is one of the hereditary blood disorders that affects the red blood cells. Several lines of evidence indicated that the vitamin D deficiency (VDD) is quite common in children with SCD and vitamin D supplementation enhanced health-related quality of life in these patients. The present study is aimed to assess the exact prevalence of VDD in SCD patients using meta-analysis.

Materials and Methods: A systematic search was conducted in PubMed and Google Scholar to extract the papers that contain prevalence data and numbers of patients with VDD in SCD patients and healthy people. Pooled prevalence was estimated using MAJOR module of Jamovi library. The overall risk ratio of having VDD in patients with SCD was calculated using the Review Manager (RevMan 5.4.1) program.

Results: A total of 26 prevalence estimates from 25 papers were included in the meta-analysis. The pooled prevalence of VDD among SCD patients is 60% (95% CIs: 50%-70%). Further, VDD is not significantly different in both SCD patients and healthy controls (risk ratio of 1.28 and 95% CI of 0.81-2.04).

Conclusion: Results of this meta-analysis indicate prevalence of VDD in SCD patients. Further, a well-designed, placebo-controlled RCTs have to be conducted to determine the effects and the safety of vitamin D supplementation in children and adults with SCD.

Keywords: Sickle cell disease, Vitamin D deficiency, Prevalence, Meta-analysis

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Introduction

Sickle cell disease (SCD) is one of the monogenic hereditary blood disorders that affects the red blood cells (1). The prevalence of SCD varies greatly across the globe. Analysis of sickle cell haplotypes supports an independent origin of SCD mutations, and haplotypes may differ in SCD severity (2). The common manifestations of SCD include extreme anemia, hemolysis, Vaso-occlusive crisis and multi-organ damage due to ischemia/reperfusion injury, organ injury, splenic sequestration, jaundice, bone dactylitis, acute chest syndrome. SCD patients also suffer from several other bone related disorder such as osteomyelitis, dactylitis and avascular necrosis of femoral head making them refrain walking (3, 4).

Vitamin D is essential for normal bone development and maintenance of healthy bones in both children and adults (5). Vitamin D not only maintains calcium and phosphate levels needed for proper growth of bone, but also plays a major role in the regulation of immune function, inflammation and cellular functions (6). Vitamin D deficiency (VDD) has been associated with osteomalacia, osteoporosis, increase risk for fractures and autoimmune disorders (7). As SCD patients exhibit lower nitrogen economy and higher protein turn over due to erythropoietic demands, these patients develop kidney failure and an increased chance of developing VDD. VDD in SCD patients progress into low bone mineral density, higher risk of bone fracture and increase risk of falls (8). Several lines of evidence indicated that vitamin D supplement in enhancing the quality of life. Compared to the general population, the prevalence of VDD is high in children with SCD. Several studies have reported the prevalence of VDD in SCD patients, but the results report broad range of variations ranging from 4% to 96% (9, 10). So, the present study is aimed to assess the prevalence of VDD using meta-analysis. Further we also analyzed the risk of VDD in sickle cell patients.

Materials and Methods

Study search and selection

This meta-analysis was conducted based on guidelines laid down in preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (11). Literature search was carried out in PubMed and Google

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Implication for health policy/practice/research/medical education

Vitamin D deficiency (VDD) is common among patients with sickle cell disease (SCD). The prevalence estimates of VDD in SCD from 26 studies were subjected to meta-analysis. The results of this meta-analysis showed that the pooled prevalence of VDD among SCD patients was 60%. As vitamin D deficiency is tightly linked with clinical complications, vitamin D supplementation should be considered by clinicians.

scholar databases. The following keywords were used "vitamin D", "25-hydroxy cholecalciferol", "vitamin D deficiency", and "sickle cell disease". The search showed 1045 studies in PubMed and 867 studies in Google Scholar. Studies satisfied the following inclusion criteria; 1) cross-sectional, cohort or case-control studies; 2) paper contains prevalence data and numbers of patients with VDD in Sickle cell Patients and healthy people; 3) papers written in the English language. We excluded studies with inadequate data to calculate prevalence and risk ratio. Two authors individually screened titles and abstracts of the papers and shortlisted 25 papers. The following outcomes of interest were extracted from all eligible studies: title, name of authors, year of study, reference value of VDD, number of VDD patients in SCD and healthy group (Table 1). The flow of study selection process is shown in Figures 1 and 2.

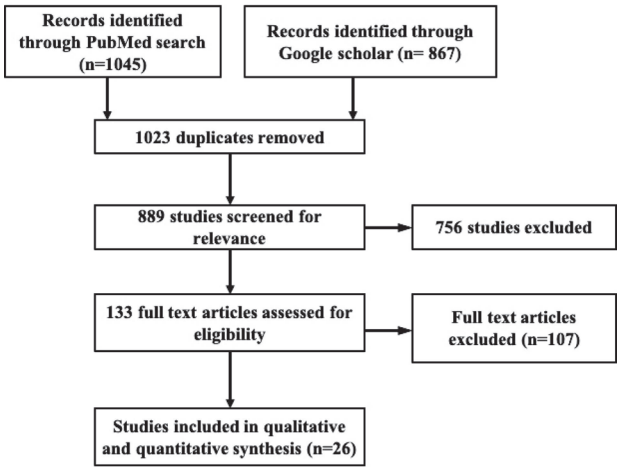

Figure 1. Flow of study selection process.

Statistical analysis

As most of the papers considered 25-hydroxyvitamin D serum level< 20 ng/mL (50 nmol/L) as VDD, we also used this level to compare the prevalence of VDD in both SCD and healthy individuals. Heterogeneity between studies was calculated by I^2 Statistics. For calculating the pooled prevalence, frequencies of the VDD and total sample sizes of each study were used. MAJOR module from Jamovi library was used for this purpose. The overall risk ratio of having VDD in patients with SCD was calculated using the Review Manager (RevMan 5.4.1) program. Publication bias was assessed by visual examination of the funnel plots.

Results

Twenty-six prevalence estimates were included in the meta-analysis. There was greater variation in prevalence estimates, which ranged from 4% in SCD patients of Canada to 96% for African SCD patients from United States. The I^2 value of 98.41% indicated high heterogeneity between studies. The overall random-effects pooled prevalence of VDD was 60% (95% CIs: 50%-70%) (Figure 3). The individual risk ratios and overall risk ratios calculated from six studies were depicted in the forest plot (Figure 4). Risk ratio of 1.28 with 95% CI of 0.81-2.04 indicates that the VDD is not significantly different in both SCD patients and healthy controls. The high level of heterogeneity (I^2 = 95%) found in this study suggests that there are discrepancies between studies. However, data seem robust with no evidence of major publication bias (Figure 5).

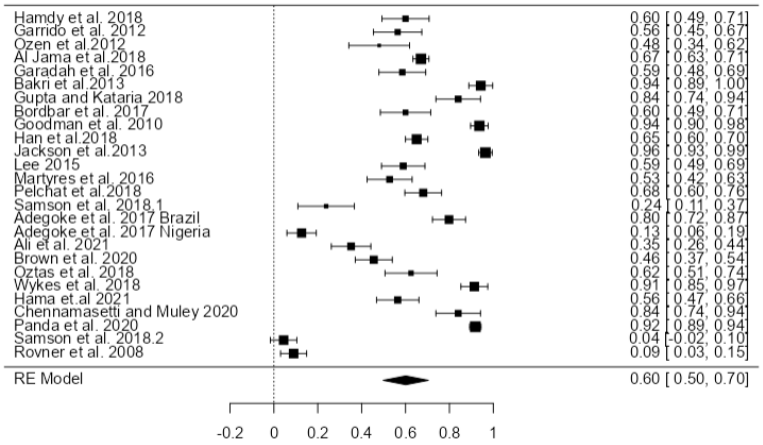

Figure 2. Forest plot depicting pooled prevalence of VDD in SCD patients.

Table 1. Baseline characteristic of studies included in the meta-analysis

Study	Country	Study design	Age group	VDD reference value	SCD patients		Healthy individuals		Ref.
					VDD	No VDD	VDD	No VDD	
Rovner et al. 2008	USA	Case control	5-18	<11 ng/mL	8	89	20	61	(12)
Goodman et al. 2010	USA	Cross sectional	21-56	<20 ng/mL	133	142	-	-	(13)
Garrido et al. 2012	Spain	Cross sectional	0-16	<20 ng/mL	44	78	-	-	(14)
Ozen et al. 2013	Turkey	Cross sectional	4-18	<20 ng/mL	24	50	-	-	(15)
Bakri et al. 2013	Bahrain	Case control	<13	<20 ng/mL	66	70	31	70	(16)
Jackson et al. 2012	USA	Cross sectional	7.9-15.1	<20 ng/mL	134	139	-	-	(9)
Wykes et al. 2014	London	Cross sectional	9.8±4.4	<20 ng/mL	74	81	-	-	(17)
Lee et al. 2015	USA	Cross sectional	2-19	<20 ng/mL	56	95	-	-	(18)
Martyres et al. 2016	Canada	Cross sectional	2-18	<20 ng/mL	48	91	-	-	(19)
Garadah 2016	Bahrain	Case control	21±5.7	<20 ng/mL	48	82	15	82	(20)
Bordbar et al. 2017	Iran	Case control	3-31	<20 ng/mL	42	70	58	70	(21)
Adegoke et al. 2017	Brazil	Cross sectional	4-11	<20 ng/mL	87	109	-	-	(22)
Adegoke et al. 2017	Nigeria	Cross sectional	7.35±2.47	<20 ng/mL	12	95	-	-	(22)
Grégoire-Pelchat et al. 2018	Canada	Cross sectional	9.2-14.8	<20 ng/mL	81	119	-	-	(23)
Samson et al. 2018	Canada	Cross sectional	2-17	<20 ng/mL	10	42	-	-	(10)
Hamdy et al. 2018	Egypt	Case control	4.3-15.5	<20 ng/mL	48	80	16	60	(24)
Han et al. 2018	USA	Cross sectional	>18	<20 ng/mL	218	335	-	-	(25)
AlJama et al. 2018	Saudi Arabia	Cross sectional	>12	<20 ng/mL	429	640	-	-	(26)
Samson et al. 2018	Canada	Retrospective chart review	2-19	<30 ng/mL	2	45	-	-	(10)
Gupta and Katariya 2018	India	Case-control	>12	<20 ng/mL	42	50	-	-	(27)
Oztas et al. 2018	Turkey	Cross sectional	2-18	<20 ng/mL	40	64	-	-	(28)
Brown et al. 2020	USA	Retrospective chart review	1-21	<20 ng/mL	61	134	-	-	(29)
Chennamasetti and Muley 2020	India	Cross sectional	>18	<30 ng/mL	42	50	-	-	(30)
Panda et al. 2020	USA	Prospective study	7.36±3.85	NA	393	428	-	-	(31)
Ali 2021	Saudi Arabia	Cross sectional	Child 5-12 Adult >12	<20 ng/mL	38	108	-	-	(32)
Hama et al. 2021	Iran	Case control	15.9±9.6	<20 ng/mL	57	61	91	110	(33)

Discussion

The results of this meta-analysis revealed that the global prevalence of VDD in patients with SCD is 60%. Further, the prevalence of VDD is not significantly different in SCD patients and healthy controls. Initial research on pediatric SCD patients found that their risk of developing VDD is 5.3 times higher than that of healthy individuals (12). This has been supported by a recent study, which found that SCD patients had a five times higher risk of VDD than the general population (15,34). Further, children with SCD-SS were at higher risk for low vitamin D status in the spring season (35). Low serum 25-hydroxyvitamin D is significantly increasing the risk of pain in SCD patients (18). Results of a randomized double blind pilot study showed that the higher serum 25-hydroxyvitamin D is beneficial in reducing the number of pain days in SCD patients (36). The significantly decreased hemoglobin and hematocrit levels found in SCD patients suggest the possibility that VDD contributes to the development of hemolysis and other SCD complications (24,37).

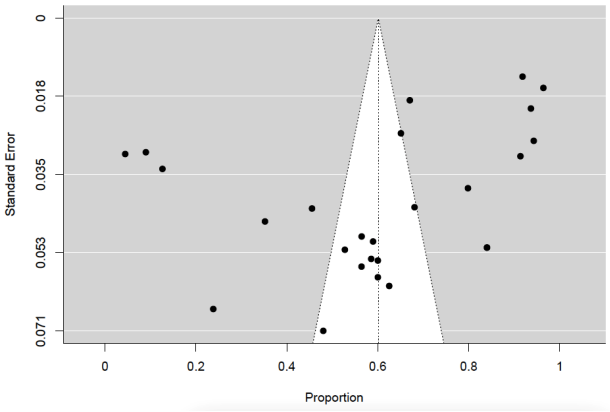

Figure 3. Funnel plot showing publication bias on prevalence of VDD in SCD patients

Vitamin D supplementation plays a vital role in reducing pain and increasing the quality of life of SCD patients. Daily oral supplementation with high doses of D3 between 4000 and 7000 IU for 6 to 12 weeks was well tolerated and significantly enhanced health-related quality of life and

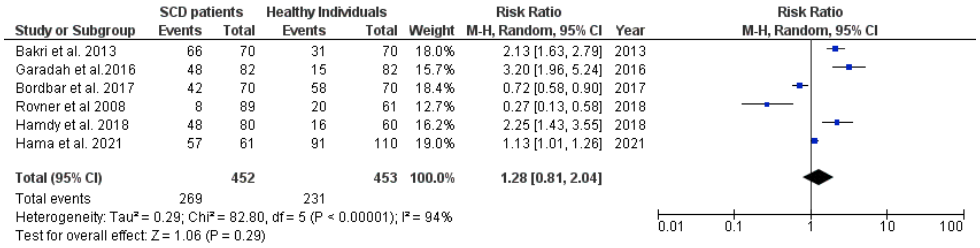

Figure 4. Forest plot showing the individual and pooled risk ratios of having VDD in patients with SCD patients.

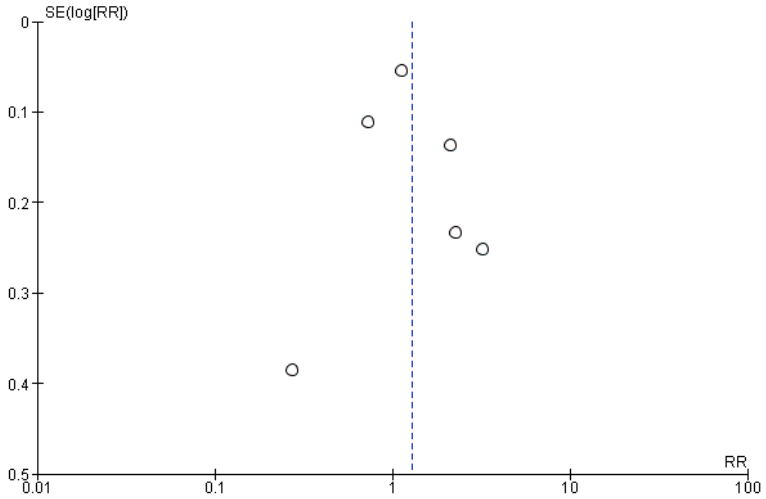

Figure 5. Funnel plot showing publication bias of studies comparing the VDD between SCD patients and healthy individuals.

physical performance in African American SCD-patients (38). A recent randomised controlled trial found that a daily dose of 1000 IU vitamin D3 and a high-dose vitamin D bolus will help SCD patients to maintain 25(OH)D levels ≥ 75 nmol/L (39).

Conclusion

The present meta-analysis made an effort to summarize the prevalence of VDD in SCD patients around the globe. Additional studies have to be designed to assess the musculoskeletal and non-skeletal effects of VDD in SCD patients. As VDD is more in SCD patients and is tightly linked with clinical complications, vitamin D supplementation should be considered by clinicians. Further, a well-designed, placebo-controlled RCTs have to be conducted to determine the effects and the safety of vitamin D supplementation in children and adults with SCD.

Authors' contribution

Conceptualization: LVKSB. Methodology: LVKSB. Resources: LVKSB. Data Curation: AS and UNP. Writing-Original Draft Preparation: AS and UNP. Writing-Review and Editing: LVKSB. Supervision: LVKSB.

Conflicts of interest

The authors declared no conflict of interest.

Ethical issues

This meta-analysis was conducted based on guidelines laid down in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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