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

Anupa Sahu*, Udit Narayan Padhi, LVKS Bhaskar

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% CI: 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

Please cite this paper as: Sahu A, Narayan Padhi U, Bhaskar LVKS. Defining vitamin D deficiency in patients with sickle cell disease; A meta-analysis. J Parathyroid Dis. 2022;10:e11154. doi: 10.34172/jpd.2022.11154.

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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
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.

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.

**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 I² 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 I² 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 (I² = 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).
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).

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

| Study                          | Country       | Study design         | Age group | VDD reference value | SCD patients | Healthy individuals | Ref. |
|--------------------------------|---------------|----------------------|-----------|---------------------|--------------|---------------------|------|
| 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) |
| Adegboke et al. 2017           | Brazil        | Cross sectional      | 4-11      | <20 ng/mL           | 87           | 109                 | -    | -                   | (22) |
| Adegboke 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) |
| Alljama et al. 2018             | Saudi Arabia  | Cross sectional      | >12       | <20 ng/mL           | 429          | 640                 | -    | -                   | (26) |
| Samson et al. 2018             | Canada        | Cross sectional      | 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 | >18 | <30 ng/mL | 61 | 134 | - | (29) |
| Chennamsetti 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) |

Table 1. Baseline characteristic of studies included in the meta-analysis
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: LVKS. Methodology: LVKS. Resources: LVKS. Data Curation: AS and UNP. Writing-Original Draft Preparation: AS and UNP. Writing-Review and Editing: LVKS. Supervision: LVKS.

Conflicts of interest
The authors declared no conflict of interest.



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.

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.

Funding/Support
None.

References
1. Risoluti R, Caprari P, Gullifa G, Massimi S, Sorrentino F, Maffei L, et al. Innovative screening test for the early detection of sickle cell anemia. Talanta. 2020;219:121243. doi: 10.1016/j.talanta.2020.121243.
2. Bhaskar LVKS, Pattnaik S. HBB gene cluster haplotype diversity in sickle cell anemia patients of Chhattisgarh, India. J Appl Biol Biotech. 2021;9:64-9. doi: 10.2478/JABB.2021.9509.
3. Malowany JI, Butany J. Pathology of sickle cell disease. Semin Diagn Pathol. 2012;29:49-55. doi: 10.1053/j.sdp.2011.07.005.
4. Verma HK, Lakkakula S, Lakkakula BVKS. Retrospection of the effect of hydroxyurea treatment in patients with sickle cell disease. Acta Haematol Pol. 2018;49:1-8. doi: 10.2478/ahp-2018-0001.
5. Holick MF, Vitamin D: a d-lightful solution for health. J Investig Med. 2011;59:872-80. doi: 10.2310/JIM.0b013e318214e2ad.
6. Shima R. The Importance and Role of Calcium on the Growth and Development of Children and Its Complications. Int J Res App Sci Biotechnol. 2020;7:162-7.
7. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutr J. 2010;9:65. doi: 10.1186/1475-
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1. Grégoire-Pelchat P, Alos N, Ribault V, Pastore Y, Robitaille N, LeMay S, Altmann DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097.

2. Rovner AJ, Stallings VA, Kawchak DA, Schall JJ, Ohene-Frempong K, Zemel BS. High risk of vitamin D deficiency in children with sickle cell disease. J Am Diet Assoc. 2008;108:1512-6. doi: 10.1016/j.jada.2008.06.043.

3. Goodman BM 3rd, Arzt N, Radford B, Chen IA. Prevalence of vitamin D deficiency in adults with sickle cell disease. J Natl Med Assoc. 2010;102:332-5. doi: 10.1016/s0027-9684(15)30605-2.

4. Garrido C, Cela E, Beléndez C, Mata C, Huerta J. Status of vitamin D in children with sickle cell disease living in Madrid, Spain. Eur J Pediatr. 2012;171:1793-8. doi: 10.1007/s00431-012-1817-z.

5. Ozen S, Unal S, Erçetin N, Taşdelen B. Frequency and risk factors of endocrine complications in Turkish children and adolescents with sickle cell anemia. Turk J Haematol. 2013;30:25-31. doi: 10.4274/tjh.2012.0001.

6. Bakri AH, Garadah TS, Jaradat AA, Al Ajmi A, Alawi ME, Sequeira RR. Prevalence of vitamin D deficiency in patients with sickle cell disease in Bahrain. Int J Med Sci. 2013;1:6. doi: 10.7150/ijms.v1i1.1126.

7. Wykes C, Arasaretman A, O’Driscoll S, Fennah L, Moniz C, Rees DC. Vitamin D deficiency and its correction in children with sickle cell anaemia. Ann Hematol. 2014;93:2051-6. doi: 10.1007/s00277-013-2144-7.

8. Lee MT, Licursi M, McMahon DJ. Vitamin D deficiency and acute vaso-occlusive complications in children with sickle cell disease. Pediatr Blood Cancer. 2015;62:643-7. doi: 10.1002/pbc.25399.

9. Martyes DJ, Vijenthira A, Barrowman N, Harris-Jans S, Chreten CJ, Klaassen RJ. Nutrient Insufficiencies/Deficiencies in Children With Sickle Cell Disease and Its Association With Increased Disease Severity. Pediatr Blood Cancer. 2016;63:1060-4. doi: 10.1002/pbc.25940.

10. Garadah TS, Jaradat AA, Alalawi ME, Hassan AB. Hormonal and echocardiographic abnormalities in adult patients with sickle-cell anemia in Bahrain. J Blood Med. 2016;7:283-9. doi: 10.2147/jbm.S124426.

11. Bordbar MR, Haghpanah S, Zarei T, Dabbaghmanesh MH, Omrani GR, Saki F. Evaluation of bone mineral density in children with sickle-cell anemia and its associated factors in the south of Iran: a case-control study. Arch Osteoporos. 2017;12:70. doi: 10.1186/s11657-017-0364-x.

12. Adegoke SA, Figueredo MS, Adekile AD, Braga JAP. Comparative study of the growth and nutritional status of Brazilian and Nigerian school-aged children with sickle cell disease. Int Health. 2017;9:327-34. doi: 10.1093/inthealth/ixv035.

13. Grégoire-Pelchat P, Zemel BS. Vitamin D Intake and Status of Children With Sickle Cell Disease in Montreal, Canada. J Pediatr Hematol Oncol. 2018;40:e531-e536. doi: 10.1097/MPH.0000000000001306.

14. Hamdy M, Salama N, Maher G, Elrefaei A. Vitamin D and Non-skeletal Complications among Egyptian Sickle Cell Disease Patients. Adv Hematol. 2018;2018:3867283. doi: 10.1155/2018/3867283.

15. Han J, Zhang X, Safa S, Gouwari M, Molokie RE, Hassan J, et al. Risk factors for vitamin D deficiency in sickle cell disease. Br J Haematol. 2018;181:828-35. doi: 10.1111/bjh.15270.

16. Alljama A, Alkhaliﬁah M, Al-Dabous AI, Alqudaihi G. Vitamin D in sickle cell disease patients in the Eastern Province of Saudi Arabia. Ann Saudi Med. 2018;38:130-136. doi: 10.5144/0256-4947.2018.130.

17. Gupta M, Kataria D. Status of vitamin-D deficiency in sickle cell disease in adults. J Evol Med Healthc. 2018;5:3137-43. doi: 10.4103/jemhc.jemhc_688_16.

18. Oztas Y, Unal S, Eskandari G, Tamer L, Ozugunes N. Vitamin D Deficiency and Its Association with Inflammatory Markers, Lipid Proﬁle and Regulatory T-cells in Pediatric Sickle Cell Disease Patients. Indian J Hematol Blood Transfus. 2018;34:480-5. doi: 10.1007/s12288-017-0890-0.

19. Brown B, Long K, Agdere L, Kutipa J, Zarzoso-Fernandez S, Choudhary D, et al. The association between vitamin D deficiency and hospitalization outcomes in pediatric patients with sickle cell disease. Blood Cells Mol Dis. 2020;82:102415. doi: 10.1016/j.bcmd.2020.102415.

20. Chenmamasseti K, Muley A. A study of Vitamin D deficiency in patients with sickle cell disease and its association with severity. Georgian Med News. 2020. 2020;7:5. doi: 10.18203/2349-3933.jgmn20200111.

21. Panda PC, Mishra NR, Sa BN, Khatau A, Kumar S, Nayak BK. Effect of vitamin D on clinical profile of sickled children: a prospective study. Indian J Child Health. 2020;7:148-51. doi: 10.32677/jich.2020.v07.i04.003.

22. Ali E, Agabha N, Mashrangi Y, Ageel M, Alsabel S, Shaddad S. Assessment of vitamin D level in children and adolescents with sickle cell disease, Jazan, KSA. World J Pharm Res. 2021;10:137-46. doi: 10.20595/wjpr2021.20843.

23. Hama AH, Shakiba E, Rahimi Z, Karimi M, Mozafari H, Abdulkarim OA. Vitamin D level, lipid proﬁle, and vitamin D receptor and transporter gene variants in sickle cell disease patients from Kurdistan of Iraq. J Clin Lab Anal. 2021;35:e23908. doi: 10.1002/jcla.23908.

24. Aidekunle MO, Dada AO, Njokkanma FO, Solarin AU, Animasahun BA, Lamina MO. Comparative Effectiveness of a Six-Week Treatment Course of Vitamin D2 and D3 in Children With Sickle Cell Anemia in Steady State With Hypovitaminosis D: A Randomized Clinical Trial. J Hematol. 2021;10:114-22. doi: 10.14740/jh817.

25. Buison AM, Kawchak DA, Schall JJ, Ohene-Frempong K, Stallings VA, Zemel BS. Low vitamin D status in children with sickle cell disease. J Pediatr. 2004;145:622-7. doi: 10.1016/j.peds.2004.06.055.

26. Osunkwo I, Ziegler TR, Alvarez J, McCracken C, Cherry K, Osunkwo CE, et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. British J Haematol. 2012;159:211-5. doi: 10.1111/j.1365-2141.2012.08978.x.

27. Mandese V, Bigi E, Bruzzì P, Palazzi G, Predieri B, Lucaccioli L, et al. Endocrine and metabolic complications in children and adolescents with Sickle Cell Disease: an Italian cohort study. BMC Pediatr. 2019;19:56. doi: 10.1186/s12879-019-1423-9.

28. Dougherty KA, Schall JJ, Bortoloso C, Smith-Whitley K, Stallings VA. Vitamin D Supplementation Improves Health-Related Quality of Life and Physical Performance in Children With Sickle Cell Disease and in Healthy Children. J Pediatr Health Care. 2020;34:424-34. doi: 10.1016/j.pedhc.2020.04.007.

29. Grégoire-Pelchat P, Pastore Y, Robitaille N, LeMay S, Chan K, 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;192:385-94. doi: 10.1111/bjh.17119.