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% 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 supplement in children and adults with SCD.

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

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 Scholar.
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.

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.

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% CI: 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).
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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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Age group</th>
<th>VDD reference value</th>
<th>SCD patients</th>
<th>Healthy individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rovner et al. 2008</td>
<td>USA</td>
<td>Case control</td>
<td>5-18</td>
<td>&lt;11 ng/mL</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>Goodman et al. 2010</td>
<td>USA</td>
<td>Cross sectional</td>
<td>21-56</td>
<td>&lt;20 ng/mL</td>
<td>133</td>
<td>142</td>
</tr>
<tr>
<td>Garrido et al. 2012</td>
<td>Spain</td>
<td>Cross sectional</td>
<td>0-16</td>
<td>&lt;20 ng/mL</td>
<td>44</td>
<td>78</td>
</tr>
<tr>
<td>Ozen et al. 2013</td>
<td>Turkey</td>
<td>Cross sectional</td>
<td>4-18</td>
<td>&lt;20 ng/mL</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>Bakri et al. 2013</td>
<td>Bahrain</td>
<td>Case control</td>
<td>&lt;13</td>
<td>&lt;20 ng/mL</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td>Jackson et al. 2012</td>
<td>USA</td>
<td>Cross sectional</td>
<td>7.9-15.1</td>
<td>&lt;20 ng/mL</td>
<td>134</td>
<td>139</td>
</tr>
<tr>
<td>Wykes et al. 2014</td>
<td>London</td>
<td>Cross sectional</td>
<td>9.8±4.4</td>
<td>&lt;20 ng/mL</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Lee et al. 2015</td>
<td>USA</td>
<td>Cross sectional</td>
<td>2-19</td>
<td>&lt;20 ng/mL</td>
<td>56</td>
<td>95</td>
</tr>
<tr>
<td>Martyres et al. 2016</td>
<td>Canada</td>
<td>Cross sectional</td>
<td>2-18</td>
<td>&lt;20 ng/mL</td>
<td>48</td>
<td>91</td>
</tr>
<tr>
<td>Garadah 2016</td>
<td>Bahrain</td>
<td>Case control</td>
<td>21±5.7</td>
<td>&lt;20 ng/mL</td>
<td>48</td>
<td>82</td>
</tr>
<tr>
<td>Bordbar et al. 2017</td>
<td>Iran</td>
<td>Case control</td>
<td>3-31</td>
<td>&lt;20 ng/mL</td>
<td>42</td>
<td>70</td>
</tr>
<tr>
<td>Adegoke et al. 2017</td>
<td>Nigeria</td>
<td>Cross sectional</td>
<td>4.3-15.5</td>
<td>&lt;20 ng/mL</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>Han et al. 2018</td>
<td>USA</td>
<td>Cross sectional</td>
<td>&gt;18</td>
<td>&lt;20 ng/mL</td>
<td>218</td>
<td>335</td>
</tr>
<tr>
<td>Aljama et al. 2018</td>
<td>Saudi Arabia</td>
<td>Cross sectional</td>
<td>&gt;12</td>
<td>&lt;20 ng/mL</td>
<td>429</td>
<td>640</td>
</tr>
<tr>
<td>Samson et al. 2018</td>
<td>Canada</td>
<td>Cross sectional</td>
<td>2-17</td>
<td>&lt;30 ng/mL</td>
<td>2</td>
<td>45</td>
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<tr>
<td>Hamdy et al. 2018</td>
<td>Egypt</td>
<td>Case control</td>
<td>4.3-15.5</td>
<td>&lt;20 ng/mL</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>Han et al. 2018</td>
<td>USA</td>
<td>Cross sectional</td>
<td>&gt;18</td>
<td>&lt;20 ng/mL</td>
<td>218</td>
<td>335</td>
</tr>
<tr>
<td>Gupta and Kataria 2018</td>
<td>India</td>
<td>Case control</td>
<td>&gt;12</td>
<td>&lt;20 ng/mL</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>Oztas et al. 2018</td>
<td>Turkey</td>
<td>Cross sectional</td>
<td>2-18</td>
<td>&lt;20 ng/mL</td>
<td>40</td>
<td>64</td>
</tr>
<tr>
<td>Brown et al. 2020</td>
<td>USA</td>
<td>Retrospective chart review</td>
<td>1-21</td>
<td>&lt;20 ng/mL</td>
<td>61</td>
<td>134</td>
</tr>
<tr>
<td>Chennamsetti and Muley 2020</td>
<td>India</td>
<td>Cross sectional</td>
<td>&gt;18</td>
<td>&lt;30 ng/mL</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>Panda et al. 2020</td>
<td>USA</td>
<td>Prospective study</td>
<td>7.36±3.85</td>
<td>NA</td>
<td>393</td>
<td>428</td>
</tr>
<tr>
<td>Ali 2021</td>
<td>Saudi Arabia</td>
<td>Cross sectional</td>
<td>Child 5-12 Adult &gt;12</td>
<td>&lt;20 ng/mL</td>
<td>38</td>
<td>108</td>
</tr>
<tr>
<td>Hama et al. 2021</td>
<td>Iran</td>
<td>Case control</td>
<td>15.9±9.6</td>
<td>&lt;20 ng/mL</td>
<td>57</td>
<td>61</td>
</tr>
</tbody>
</table>

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

**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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**References**


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