original article

Vitamin D deficiency in sickle cell disease patients in the Eastern Province of Saudi Arabia

Ali AlJama,[a] Mohammed AlKhalifah,[b] Ibrahim Abdulla Al-Dabbous,[c] Ghada Alqudaihi[d]

From the [a]Department of Internal Medicine; [b]Department of Laboratory; [c]Department of Pediatrics; and [d]Department of Epidemiology, Qatif Central Hospital, Qatif, Saudi Arabia

Correspondence: Ali AlJama · Department of Internal Medicine, Qatif Central Hosptal, PO Box 627, Qatif 31911, Saudi Arabia · T: 966-13-855-5927 · aaljama.im@gmail.com · ORCID: http://orcid.org/0000-0002-9985-7666

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BACKGROUND: Vitamin D deficiency (VDD) is a major global health problem. In sickle cell disease (SCD), VDD is highly prevalent, reaching up to 96% of populations. VDD may contribute to many of the complications of SCD.

OBJECTIVE: Estimate the 25-hydroxyvitamin D [25(OH)D] level and the frequency of VDD and insufficiency among among SCD patients by age group and disease status.

DESIGN: Analytical cross-sectional.

SETTING: Ministry of Health (MOH) secondary care hospital.

PATIENTS AND METHODS: Non-probability purposive sampling was used to select SCD patients, aged 12 years and older, of both sexes, who had visited the hospital during a period of 5 years (2010-2014). Blood samples were processed by electrochemiluminescence technology.

MAIN OUTCOME MEASURE(S): 25(OH)D levels by demographic data, and disease activity.

SAMPLE SIZE: 640 patients.

RESULTS: Of those, 82% (n=523) had suboptimal 25(OH)D (0-<30 ng/mL), and 67% were deficient (0-<20 ng/mL). Patients with any SCD crisis (20.7%, 144/694) had lower 25(OH)D (median, IQR: 10.1 ng/mL [8.6] ng/mL) compared to patients without crisis (71.0%, 493/694) (15.7 ng/mL [18.2] ng/mL) (*P*<.001). Deficiency was more common in the younger age groups and in sickle cell anemia patients with crisis.

CONCLUSIONS: VDD is highly prevalent in this population. Established vitamin D screening is a necessity, so that affected patients can be treated.

LIMITATIONS: Presence of residual confounders such as nutritional status, physical activity, lack of sun exposure, medications that alleviate SCD crises (such as hydroxyurea), and comorbid illnesses. The relationship between sickle cell disease genotype and vitamin D level was not analyzed.

CONFLICT OF INTEREST: None.

Vitamin D is vital for bone health as well as maintenance of normal serum calcium and phosphate levels.[1] Furthermore, vitamin D may play an important role in immune function, cell proliferation, differentiation, and apoptosis. Vitamin D deficiency (VDD) has been associated with numerous health problems. The most obvious clinical conditions associated with VDD are skeletal disorders such as rickets in children, and osteomalacia in adults. Other clinical conditions associated with VDD include an increased risk of fractures, falls, cancer, autoimmune disease, and increased risk of infections.[1] VDD is recognized as a major health problem worldwide.[2] Even in regions with year- long adequate sunlight, VDD is prevalent.[3] For example, several studies have shown that VDD is highly prevalent in different areas of Saudi Arabia.[4-12]

Among sickle cell disease (SCD) patients, VDD is also highly prevalent.[13-16] VDD in SCD presents a challenge to the caring physician as it can cause confusion in the clinical presentation. Muscle and bone pain may mimic acute sickle cell pain or chronic pain syndrome.[17] Also, some bone complications of SCD may be caused or at least exacerbated by VDD.[18,19] SCD in the Eastern Province of Saudi Arabia is different from the African type. A unique haplotype called the "Arab-Indian" haplotype (also called the Asian or Saudi haplotype) is present in the Eastern Province.[20] Because of the high prevalence of VDD in this region, an effective vitamin D screening and treatment program is needed. The aim of this study was to determine the 25-hydroxyvitamin D [25(OH)D] level in SCD patients and the frequency of VDD and insufficiency. We also intended to increase the awareness of caregivers of these patients and the importance of early diagnosis and management. To our knowledge this is the first study to address the vitamin D status and the frequency of VDD in a fairly large sample of SCD patients in the Eastern Province of Saudi Arabia.

PATIENTS AND METHODS

Our cross-sectional study took place in a single health care center, Qatif Central Hospital, the main governmental secondary care institute in Qatif city. Qatif is located in the Eastern Province of Saudi Arabia, at latitude 26.565191 N.[21] The hospital is one of three main institutes in the province that serves almost all of the SCD population whether in an acute or chronic disease status. It is estimated that 2.6%[22] of the total Qatif population (455 811)[23] are born with SCD.

An initial 25(OH)D level screening for all SCD patients was performed, regardless of their disease status, as part of their routine comprehensive assessment. A non-probability purposive sampling technique was used (the entire SCD population that attended the clinical care areas of Qatif Central Hospital, and fit the specified case definition were recruited). Cases were defined as any SCD patient confirmed by hemoglobin electrophoresis, regardless of disease status (steady state or with any SCD crisis), of all genotypes, aged 12 years and older, and of either gender who had visited the hospital. The recruitment took place in the following areas: outpatient (i.e. emergency room, and both medical and hematology clinics) and inpatient (i.e. teen and adult medical wards) during the period of 1 January 2010 to 31 December 2014. The age of 12 years and above was chosen because MOH regulations adopt age 12 years as the cutoff point between children and adults. The initial vitamin D reading was used for all patients; any other vitamin D results of patients with multiple readings were excluded. The exclusion criteria included children aged <12 years, patients with known previous VDD, patients with a history of vitamin D, or current vitamin D treatment, and sickle cell traits. Recruitment of SCD patients took place across both dry and wet seasons.

A blood sample (fasting not mandatory) was taken from each patient using a standardized protocol. Blood specimens were immediately processed to separate serum by centrifugation at 3500g for 5 minutes. The sera were analyzed or stored at 2-8°C till processing. The samples were processed using electrochemiluminescence technology (Cobas machines; COBAS 6000 C501 Analyzer manufacturer: Hitachi High-Technologies Corporation, Tokyo, JAPAN, authorized representative was Roche Diagnostics GmbH Germany) to find the level of 25(OH)D. The 25(OH)D level was classified as follows: sufficiency (normal) was defined as a 25(OH)D level of ≥30 to 60 ng/mL (≥75-150 nmol/L), insufficiency as 20 to <30 ng/mL (50 to <75 nmol/L), and deficiency as <20 ng/mL (<50 nmol/L).[24,25] Three more subcategories were adopted for clinical and scientific correlation with disease status: suboptimal included both deficiency and insufficiency as <30ng/mL (<75 nmol/L), severe deficiency as <10 ng/mL (<25 nmol/L), and above normal as >60-150 ng/L (>150-375 nmol/L].

The Medica Plus system, a computerized health informatics system, was the primary source for data. The collected data included patient demographics, which included medical record number, age, and gender, and 25(OH)D levels, diagnosis (any of the following diagnoses was considered as SCD: sickle cell disease, sickle cell anemia, sickle cell beta-thalassemia, sickle cell disease with alpha-thalassemia) and disease status (sickle cell disease with any disease crisis or without crisis).

Table 1. Frequencies and 25-hydroxyvitamin D levels of evaluable sickle cell disease patients (n=640).

	Frequency	Vitamin D level (ng/mL)
Gender		
Female	399 (62.3)	14.6 (20.2)
Male	241 (37.7)	13.9 (11.1)
Age groups (years)		
Adolescents (12-<18)	107 (16.7)	12.0 (13.0)
Adults (18-<45)	419 (65.5)	13.3 (14.9)
Middle age (45-<65)	111 (17.3)	21.7 (24.9)
Elderly (>65)	3 (0.5)	35.4 (12.6)
SCD activity		
Sickle cell disease	49 (7.7)	16.3 (15.4)
Sickle cell anemia without crisis	463 (72.3)	10.1 (8.6)
Sickle cell anemia with crisis	128 (20)	15.7 (18.2)

Data are median (IQR) or number (percent).

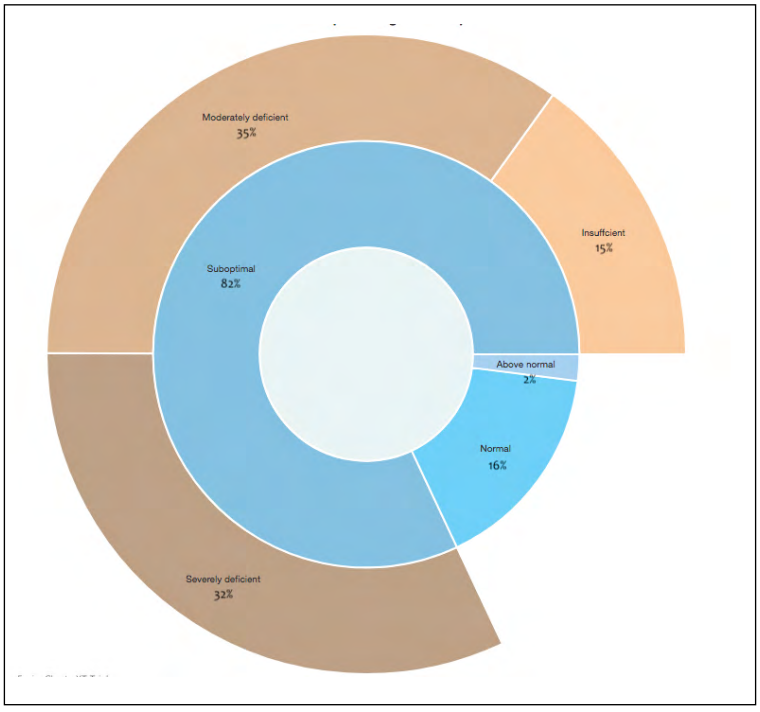

Figure 1. Serum 25-hydroxyvitamin D levels among evaluable sickle cell disease patients (n=640).

Descriptive characteristics are presented as mean and standard deviation (SD) for continuous variables and as frequencies for categorical variables. 25-(OH) D mean values with 95% confidence intervals (CI) were calculated, and a *P* value of <.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 21 (*https://www.ibm.com/products/spss-statistics*) and the R statistical computing language (version 3.4.4). Because the sample was not of the general population and thus the serum vitamin D data was heavily skewed, the median and interquartile range and the Scheirer-Rare-Hare, a nonparametric test, was used in the analysis.

The protocols for this study were reviewed and approved by the local Scientific and Ethical Committee review board (SREC) at Qatif Central Hospital Research Protocol # 41/34/165442. The consent obtained from all participants consisted of the initial general consent for hospital care which includes vitamin D screening, as part of their comprehensive care.

RESULTS

Of 694 confirmed Saudi SCD patients, vitamin D readings in 54 were inconclusive and not evaluable because the quantity of blood was insufficient or there was an error in reading, leaving 640 (92.2 %) patients that were evaluable. In the entire population of SCD patients (n=694), females were the majority (n=441, 63.5%) and most of the population was younger than 45 years (n=577, 83.1%). Middle aged and elderly patients had higher 25(OH)D levels than younger patients (*P*< .001). Although SCD females had a slightly higher 25(OH)D mean levels compared to males, the difference was not statistically significant (*P*=.106). Sickle cell anemia (SCA) patients 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 SCA patients with crisis (10.1 [8.6] ng/mL) versus SCA patients without crisis (15.7 [18.2] ng/mL) (*P*<.001).

All but 49 of the 640 evaluable patients had sickle cell anemia with or without crisis (n=591) (**Table 1**). The mean (SD) age in years of the evaluable population was 31.9 (12.7) (range, 13 to 80), and females were older than males (33.4 [12.9] vs 29.5 [12.2]).

Most of the evaluable patients (82%) had suboptimal 25(OH)D (**Figure 1**). A large proportion of those (67% of the evaluable patients) were also deficient in vitamin D (<20 ng/mL). SCA patients in steady state (i.e. without crisis) had a higher 25(OH)D levels, especially the elderly (>65 years) (**Figure 2**) and the difference across age groups was statistically significant (*P*<.001) (**Figure**

3). However, there were only three patients in the elderly group. Most of younger patients were deficient in vitamin D in both the with and without crisis groups. In patients with crisis, 25(OH)D the levels were statistically similar across the three age groups with the adult group (18-<45) accounting for most of the deficient patients (n=83 vs 19 in the other age groups).

DISCUSSION

The emergence of vitamin D hypovitaminosis in the general population of a sunny, dry country such as Saudi Arabia approaches 100% in some reports.[1,4, 6,10] This is consistent with the generally accepted notion that VDD is a pandemic health problem, inclusive of areas with year-long sun shine. With a definition of inadequate 25(OH)D level as <30 ng/mL, the frequency ranges from 5% in male Jordanians up to >97% in India.[26] Many studies have reported a high frequency of VDD in the SCD population of different haplotypes as opposed to the non-SCD population, in study specific control groups.[13-16] Nevertheless, when compared to the healthy general population of the same ethnic group, the frequency was not much different in the SCD population.[14] This explanation is consistent with the finding in the present study, as SCD in the Eastern Province of Saudi Arabia is of the Arab-Indian haplotype,[20] whilst being of the same ethnicity. The present study showed a high frequency of suboptimal 25(OH)D (insufficiency and deficiency) in SCD patients, reaching 82%, which is comparable to other studies where the frequency reached up to 96%.[13-16]

Two published articles discussed the frequency of vitamin D level in relation to SCD patients in Saudi Arabia, in two different regions.[27,28] One was conducted in the southern region of Saudi Arabia,[27] where patients carry the African SCD haplotype. The study estimated that 12% of surveyed SCD patients had severe vitamin D deficiency where their serum 25(OH)D level was <10 ng/mL. A second study in the Eastern Province estimated 92% of female, and 70.9% of male SCDP had VDD defined as 25(OH)D level <20 ng/mL.[28] Our results were consistent with the results of the second study, as our patients had the same SCD background, and adopted the same VDD definition. Moreover, the large sample size of patients included in the present study, with most in a steady state without crisis, is more representative of the SCD population in the Eastern Province. Therefore, our study might allow for drawing more scientifically sound conclusions and recommendations. The over-representation of the female gender is not unusual. That can be explained by the finding that females constituted 59.5% of visitors to the outpatient department

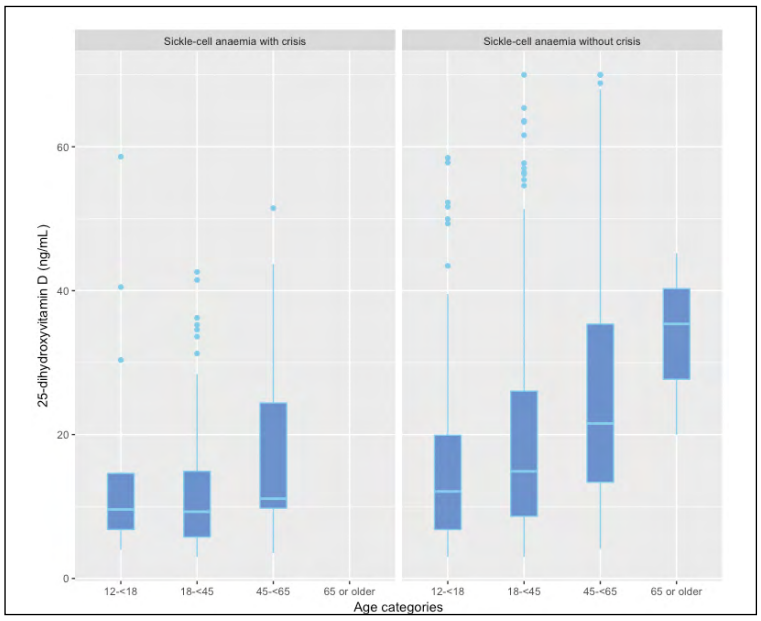

Figure 2. Serum 25-hydroxyvitamin D levels (median, first and third quartiles) by disease state and age category (n=590, excluding 1 outlier). (*P*<.001 by Scheirer-Ray-Hare test for nonparametric data).

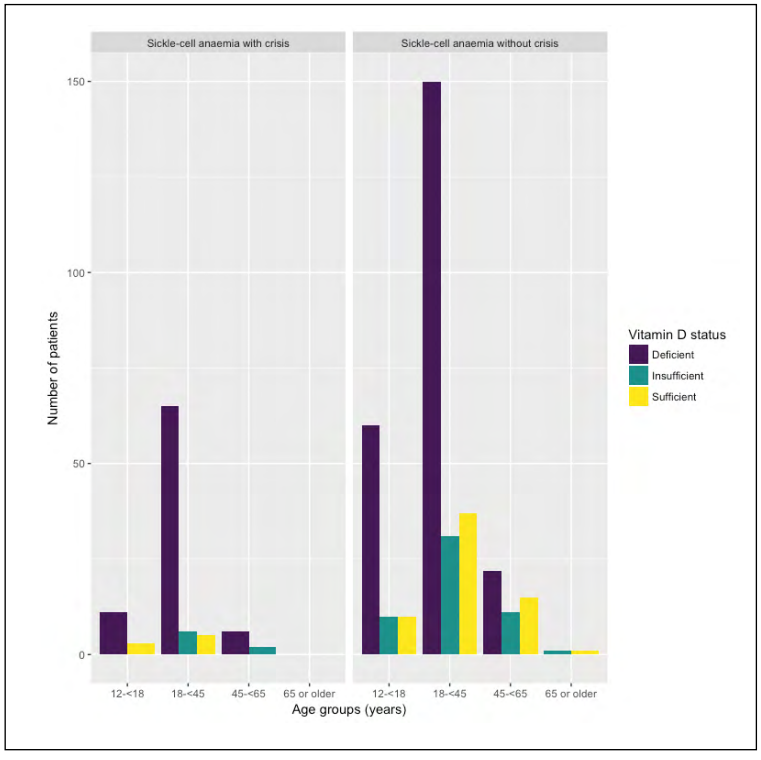

Figure 3. Distribution of vitamin D status among sickle cell anemia patients with and without disease activity (crisis vs no crisis) by age group (n=591).

(a search through our health information system over the span of one year-2015, unpublished). This was also found by other investigators.[5,29]

Our study also showed that the severity of VDD was more noticeable in SCD patients during crisis compared to patients in their steady state condition. This intriguing finding has not been found in the medical literature. It can be interpreted in two different ways. The first might indicate that VDD patients suffer from a more severe disease form and present with more sickle cell crises. That would make them more frequently encountered in the hospital and more likely to be screened during crisis. The second way concerns the presence of unique factor(s) that would interfere with the analysis of vitamin D resulting in a lower level of 25(OH)D. The second explanation was found in a similar scenario in patients with rheumatoid arthritis. In several studies 25(OH)D level was found to be negatively associated with disease activity.[30-32] and some authors suggested that the 25(OH) D level may decrease in the setting of acute or chronic inflammation, with high inflammatory cytokines, which cause a decline in vitamin D binding protein.[33-35] There is evidence that inflammation plays a role in the pathophysiology of SCD.[36,37] Altered inflammatory cytokines have been documented both in steady state and during acute vaso-occlusive crises.[38,39] This might explain the significantly low vitamin D levels during sickle cell crisis and in rheumatoid arthritis patient with active disease. It may also explain the finding that 25(OH)D levels are not different among different age groups, as the causes of low 25(OH)D levels are analytic factors. Further studies to confirm this interesting finding are needed.

Despite the fact that suboptimal 25(OH)D levels are not unique to SCD, the consequences are clinically important. There appears to be substantial overlap between the symptoms of chronic pain seen in SCD and VDD, as both disorders cause deep-seated, dull and achy pain, exacerbated by weight-bearing and commonly involving the lower spine, pelvis and extremity bones.[40,41] This may cause under-recognition of VDD in SCD patients, and misdiagnosis of chronic or even recurrent mild to moderate aches and pains as SC-related pains. The resultant health and economic consequences cannot be overemphasized. The association of VDD and chronic pain, osteoporosis, and possibly osteonecrosis in SCD was proposed in many studies.[17,28,42] That was further supported by resolution of chronic pain and improvement of bone density by treatment with vitamin D in high doses.[43,44] The effect of VDD on frequency of acute painful crises has not been proven.[17,45] Only one study suggested a potential association with acute pain.[46] VDD may be associated with other comorbidities that are common in SCD patients like bronchial asthma, abnormal lung functions and nephropathy.[47,48]

In SCD, there are causes of VDD that may be disease related involving the intestine, the liver, and the kidney.[49-52] SCD patients suffer frequently from crisis, during which they are sick and can be confined to home, at the emergency department or admitted to hospital. These factors play a role in affecting patient appetite, decreasing food intake, and decreasing exposure to sunlight, and therefore, precipitating VDD. Another factor that may contribute to VDD in our population is the traditional veil women wear which may play a role in preventing enough exposure to the sunlight needed for the synthesis of vitamin D. Our study rejects this factor, as it was found that the mean vitamin D levels in males trended towards a lower level than females (17.5 vs 19.4, consecutively), though not statistically significant (*P*=.106). This finding can be explained in that male patients may have other causes of VDD, like being more anemic, having a higher BMI, or having more liver or kidney disease; these factors were not investigated in this study. Age may be another contributing factor for VDD. Our study showed that vitamin D levels were lower in adolescents and young adults. This finding is interesting and was found in a study on both children and adults with SCD[53] which showed that vitamin D levels trend downwards in children. In adults, an opposite trend was observed. The younger age group is usually the most active age, and may require more vitamin D. In addition, the less healthy food eaten by adolescents may be deficient in vitamin D.

Our study has a few limitations including the presence of residual confounders such as nutritional status, physical activity, lack of sun exposure, use of hydroxyurea and comorbid illnesses such as chronic kidney disease, gastrointestinal disease and obesity. Additionally, results in elderly patients are not conclusive, due to the small sample presentation, demonstrating the need for further studies on this age group. Moreover, the relationship between sickle cell disease genotype and vitamin D level was not measured.

In conclusion, vitamin D hypovitaminosis in SCD may not be receiving sufficient attention due to overlaps in clinical presentation. The consequences of this health problem are clinically very important. The finding of significantly lower vitamin D levels during SC crisis needs further elucidation. A number of possible causes were proposed, but the exact mechanism remains unclear. It may contribute to various manifestations of SCD. The frequency of suboptimal vitamin D in children and adults with SCD in the Eastern Province of Saudi Arabia is very high, especially in adolescents and young adults.

Treatment of VDD in SCD patients may improve their well-being. There is a definite need for screening all patients with SCD for vitamin D hypovitaminosis, and for treatment of affected patients. Further studies of the pathophysiology and consequences of VDD in SCD are needed. This study, as other studies, emphasizes the need for vitamin D level screening for all SCD patients. Treatment of the vitamin D hypovitaminosis and maintenance with vitamin D doses meeting the daily requirements should be ensured. The direct relationship between 25(OH)D level and SCD activity status needs further analytical study. The impact of potential confounders needs to be addressed in prospective studies.

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