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Assessing Bone Mineral Density in Sickle Cell Disease Patients and linking it to Admission Rates: A Prospective Uni-center Study

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Abstract:

INTRODUCTION: Sickle cell disease (SCD) is an inherited autosomal recessive disorder with bone mineral density (BMD) as a common clinical manifestation of SCD. With a prevalence of 2.6%, Saudi Arabia is among the highest incidence of SCD worldwide. The purpose of this research was to examine how SCD evolves and how it affects bone density in Saudi patients from an Eastern Province tertiary hospital.

METHODS: This was an observational prospective study conducted in the tertiary care hospital among 119 SCD patients. Patients were divided into two groups: Group A – severe SCD patients requiring hospital care ≥3/year; and Group B included patients with a smooth course of SCD who did not require frequent hospitalization (<3 hospitalizations per year), with a milder course of the disease. Analysis was based on the frequency of hospitalizations with pain crises and measuring BMD.

RESULTS: Of 119 patients, 73.1% had low bone density. Compared to the femur (47.9%), the spine (62.2%) had a higher prevalence of low bone density. The prevalence of low BMD did not significantly differ between the two groups (64.8 vs. 79.9%, P = 0.081). Patients with more frequent hospital visits had significantly higher Mg concentrations (2.30 vs. 0.84, P = 0.001), higher gamma-glutamyl transferase (59.44 vs. 39.49, P = 0.030), and significantly lower 25-hydroxy Vitamin D (34.82 vs. 49.48, P = 0.004).

CONCLUSIONS: Patients with SCD had a generally higher prevalence of low BMD. Further research is needed to answer the proposed debate about the accuracy of DXA scanning in patients with SCD.

Keywords:

Bone mineral density, DXA scan, hydroxyurea, osteopenia, osteoporosis, sickle cell disease

Introduction

Herrick initially reported sickle cell disease (SCD) in 1910. It is an inherited autosomal recessive disorder carried on by a single base-pair point mutation in the β-globin gene that causes valine, an amino acid, to replace glutamic acid in the β-globin chain.[1,2] Because of the presence of fetal hemoglobin (Hgb F), patients are asymptomatic for the first 6 months of life. However, this gradually decreases and sickle hemoglobin (Hgb S) starts to predominate. Decreased bone mineral density (BMD) is a common clinical manifestation of SCD, which may be acute or chronic.[3-5] The acute condition includes a painful vaso-occlusive crisis (VOC), osteomyelitis, stress fracture, vertebral

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collapse, and bone marrow necrosis. The chronic condition manifests as osteonecrosis, arthritis, osteoporosis, and growth failure.[6,7]

Pregnancy-related physiological changes, like elevated metabolic demand, raise the risk of SCD complications. As a result, placental VOC can impair uteroplacental circulation, resulting in chronic hypoxia in the fetus and unfavorable outcomes for the fetus. Nonetheless, it is likely that Hgb F will protect *in utero* if patients experience no symptoms for the first 6 months of life as a result of it.[3-5] When VOC occurs, it can cause ischemia and hypoxia, damage to tissue and blood vessels, inflammation, and the release of inflammatory mediators, all of which can trigger nociceptors. VOC is a common manifestation of SCD.[8-10] Even though the pain can be felt anywhere in the body, patients most frequently report it in the back, pelvis, chest, abdomen, and long bones. Basically, acute pain can start as early as 6 months of age and keep coming back for the duration of the patient's life. The frequency of VOS in conjunction with acute chest syndrome (ACS) is the most prevalent predictor of death in SCD patients.[10-12]

SCD is a Hb disorder that is characterized by low levels of calcium and Vitamin D, an increased rate of BMD decline, and severe acute and chronic pain as well as end-organ damage throughout life.[13,14] Knowing the pathogenesis and pathophysiology of SCD is essential for selecting the best course of treatment development and intervention, as clinical manifestations of the disease can differ and it can affect any organ in the body, resulting in a reduced life expectancy.[15-17] While 80% of adults with SCD have low BMD, the mechanism (s) of bone disease in SCD is not fully understood and varies by factors such as region, age, gender, and menopausal status of patients.[18,19]

Sub-Saharan Africa, South Asia, the Middle East, and the Mediterranean have high rates of SCD. Among those, most affected by the disorder are Saudis, with 45,100 adults and 2400 children and adolescents per 1,000,000 people.[20,21] The Kingdom of Saudi Arabia (KSA) has one of the highest rates of SCD in the world, where up to 2.6% of the population is affected, with more prevalence in the Eastern and Southwestern provinces of the country.[22] Considering the global controversy regarding the impact of SCD on bone density, its relationship with the demographics of patients and the environment, as well as the high incidence of SCD in Saudi Arabia, this study aims to investigate the course of SCD and its impact on bone density in Saudi patients from a tertiary care hospital in the Eastern Province. The primary endpoint is the measuring BMD in patients with SCD. The secondary endpoint is to examine its association with hospitalization rates in patients with SCD and whether the results of the DXA scan affect the rate of hospitalization.

Methods

Study design and setting

This was an observational prospective study conducted at King Fahd Military Medical Complex Tertiary Care Hospital in Dhahran, Eastern Province, KSA. The study included $n = 119$ SCD patients requiring hospitalization for sickle crisis or outpatient examination between May and December 2022. Some of the patients included in the study were recruited from the outpatient hematology clinic because they were not hospitalized during the study period but met the inclusion criteria based on medical records.

Participants

The eligibility criteria were:

- Inclusion criteria – known to have SCD of any genotyping Hgb SS, HgbSB thal, HgbSC, HgbSE, HgbSD, and HgbS-O; both genders; older than 14 years; had complete file record including their chemistry result; nationality – Saudi.
- Exclusion criteria – non-SCD patients; patients with active crisis (patients in active crisis were excluded. Patients with SCD may experience acute episodic pain, and some may experience chronic pain, which is a minority occurrence at our center. DXA was not performed in cases of active pain, either acute or chronic, because it could be uncomfortable for the patient and the blood supply to the area to be examined could be compromised during an active crisis); patients on steroid or hormone therapy; the pediatric age group under the age of 14 (in accordance with the hospital's pediatric age group policy); and pregnant women.

Procedures

The study was conducted following ethical approval from the Eastern Province Armed Forces Hospital Institutional Review Board (AFTER-IRB-2022-017, May 12, 2022). Patients provided their written informed consent to participate in the research after the aim and objectives of the research were thoroughly explained. All patients agreed to undergo DXA scanning. This study complies with the Declaration of Helsinki.

Data collection

The patients were divided into two groups. Group A included patients with severe SCD requiring care for three or more admissions per year. Group B included patients with a smooth course of SCD who did not require frequent hospitalization (<3 hospitalizations

per year), with a milder course of the disease and better blood circulation. As a result, higher blood flow to bone tissue and less bone resorption were expected, and DXA scanning could provide a better result compared with Group A with frequent hospitalization and poor circulation.

Clinical, laboratory, and radiological data were obtained and prospectively tracked through the electronic recording system. Comparison between the two groups was based on the frequency of hospitalizations with a pain crisis and the presence of a low BMD score. When assessing BMD, the lumbar spine (L1-L4) and the femoral neck were scanned using DXA. Data on age, gender, comorbidities, drug treatment, and need for blood transfusions were documented. In addition to hemoglobin levels and hemoglobin electrophoresis, biochemistry results were collected, including calcium, magnesium, phosphate, thyroid, parathyroid, and 25-hydroxy Vitamin D (25(OH) D) levels.

A blood sample was collected in an ethylenediaminetetraacetic acid tube for hematological examination and parathyroid hormone assessment, and a heparin tube (sodium/lithium/ammonium) for the collection of other biochemical tests. For total chemical composition, including calcium, magnesium, and phosphate, the sample was analyzed using a Dimension RxL Max instrument (Siemens). For thyroid function and Vitamin D levels, the sample was analyzed using the Alinity I device (Abbott), and for parathyroid hormone, the sample was analyzed using the Liaison XL device (DiaSorin). Technical procedures were in accordance with the international standards.

BMD was measured through a dual X-ray absorptiometry model (Hologic Discovery Wi) using Hologic Apex software (version 3.3.0.1, copyright (C) 2011 Hologic Inc.). The lumbar spine (L1-L4) and hip (left femoral neck) were measured and recorded. Reporting of densitometry (DXA) scan was used as recommended by the International Society for Clinical Densitometry. This study used a *Z*-score rather than a *T*-score because the *T*-score is mainly used in postmenopausal women and men over 50 years of age, which is not applicable to this group of patients.[23,24] Based on the *Z*-score, patients were classified as having normal or low BMD in a specific body area studied; score <−2.0: below expected range/low bone density for age; and score ≥−2: interpreted as within the expected range.[23,25] Further evidence suggests that if there is a fracture, it may be associated with osteoporosis, while the absence of a fracture does not indicate osteoporosis or osteopenia using a DXA scan. In this condition, it may only represent a normal or abnormal BMD test.[23-26] No additional adjustment was made other than the international standard DXA adjustment.[26] The result was interpreted based on the World Health Organization criteria for the diagnosis of osteoporosis.

Statistical analysis

MS Excel was used for data entry, cleaning, and coding. The Statistical Package for the Social Sciences (SPSS version 26, Armonk, NY: IBM Corp, USA) was used to analyze the data. While mean (M) and standard deviation (SD) were used to characterize continuous variables, frequency (n) and percentage (%) were used to characterize categorical variables. A paired *t*-test was used to test differences between the mean and SD of groups A and B. To compare categorical variables between groups A and B, Chi-square was utilized. When testing for genotype, family history, and annual admission, Fisher's exact test was utilized if the Chi-square assumption was not satisfactory. The table

Table 1: The demographic factors of patients of each group

	Group A	Group B	*P*
Age (mean±SD)	26.98±9.60	28.51±11.60	0.442
Gender			
Male	25 (46.3)	29 (44.6)	0.855
Female	29 (53.7)	36 (55.4)	
Hydroxyurea			
No	14 (25.9)	30 (46.2)	0.023*
Yes	40 (74.1)	35 (53.8)	
Genotypes			
SCD	51 (94.4)	58 (89.2)	0.486
SC/Thal	3 (5.6)	6 (9.2)	
SC/other	0	1 (1.5)	
Family history of bone diseases			
No	54 (100.0)	63 (96.9)	0.194
Yes	0	2 (3.1)	
Present of another comorbidity			
Yes	11 (20.4)	11 (16.9)	0.630
No	43 (79.6)	54 (83.1)	
Admission/year			
0	0	34 (52.3)	<0.001*
1	0	14 (21.5)	
2	0	17 (26.2)	
3	24 (44.4)	0	
>3	30 (55.6)	0	
Complication			
No	15 (27.8)	40 (61.5)	<0.001*
Yes	39 (72.2)	25 (38.5)	
BMI			Total BMI, *n* (%)
Underweight	10 (18.5)	16 (24.6)	26 (21.8)
Normal weight	36 (66.7)	34 (52.30)	70 (58.8)
Overweight	8 (14.8)	11 (16.9)	19 (16)
Obese	0	4 (6.2)	4 (3.36)

*Significant at *P*<0.05. t-test used for age. The Chi-square was used for the categorical variables. Fisher's exact test was used for genotypes, family history, and number of admissions per year. BMI: <18.5 (underweight); 18.5–24.9 (normal weight); 25–29.9 (overweight); >30 (obese) as per CDC. SC=Sickle cell; Thal=Thalassemia; BMI=Body mass index; CDC=Centers for disease control and prevention; SD=Standard deviation; SCD=Sickle cell disease

footnotes for each variable included a description of the statistical test that was used.

Results

This research was a prospective observational study with the participation of n = 119 patients with SCD, of which n = 54 were male and n = 65 were female [Table 1]. Group A included n = 54 patients, and Group B n = 65 participants. In Group A, 44.4% of patients needed three admissions per year, and 55.6% needed more than three admissions per year. In Group B, 21.5% needed one visit per year and 26.2% needed two hospital visits per year. No significant differences were found between groups in either age (P = 0.442) or gender (P = 0.855), although the participants in Group B were slightly older than Group A (28.51 versus 26.98 years) [Table 1]. The prevalence of hydroxyurea use was significantly higher in Group A (74.1%) than in Group B (53.8%) (P = 0.023). There were no significant differences between patients of both groups in terms of SCD genotype (P = 0.486), family history of bone diseases (P = 0.194), and the prevalence of additional comorbidities (P = 0.630) [Table 1]. Chronic kidney disease, divalent metal transporter 1, hypothyroidism, and growth hormone deficiency were some of the comorbidities reported among patients. The prevalence of complications among patients in Group A (72.2%) was higher than in Group B (38.5%) (P < 0.001) [Table 1]. Body mass index (BMI) is described as categorical variables which shows an almost identical distribution of BMI: 58.8% had normal BMI, only 3% were obese, and 21.8% of cases were underweight with no significant difference according to this classification between both groups [Table 1].

Complications of SCD, as in any type of crisis, included pain, hemolysis, aplastic, sequestration, ACS, and central nervous crisis [Figure 1]. ACS was the most common complication reported among n = 32 (26.89%) patients, followed by avascular necrosis (AVN) n = 20 (16.8%) and central nervous system complications n = 11 (9.2%) [Figure 1].

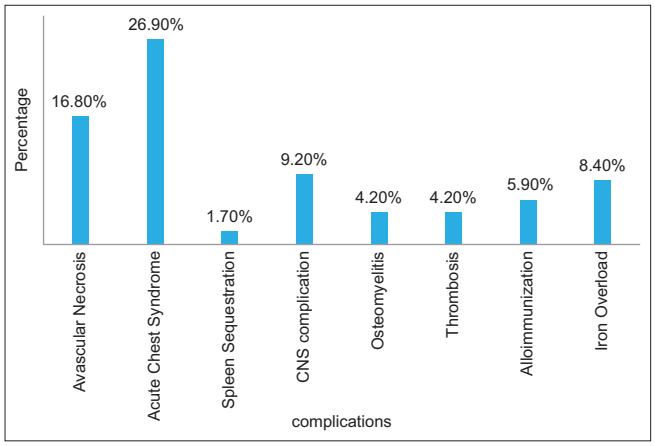

Figure 1: Type of complications among patients with sickle cell disease. CNS = Central nervous system

The M (SD) of the concentration of minerals and hormones is presented in Table 2. No significant difference was reported considering the concentration of Hgb S (75.6 vs. 74.39, P = 0.508), calcium (2.25 vs. 2.23, P = 0.461), phosphate (1.36 vs. 1.40, P = 0.476), ALP (113.76 vs. 104.11, P = 0.386), TSH (2.01 vs. 2.20, P = 0.470), and PTH (7.59 vs. 6.87, P = 0.423) between the two groups [Table 2]. However, patients with more frequent visits to hospitals (Group A) showed a significantly higher concentration of Mg (2.30 vs. 0.84, P = 0.001), a higher level of gamma-glutamyl transferase (GGT) (59.44 vs. 39.49, P = 0.030), and significantly lower concentration of 25(OH) D (34.82 vs. 49.48, P = 0.004) [Table 2].

The patients had different sites tested with DXA, i.e. the femoral neck and the spine. The percentage in each group was calculated in comparison to the total group size. General pain was observed in 31.9% of patients. The share of general pain was significantly higher in patients with more frequent visits to the hospital (42.6% vs. 23.1%, P = 0.023). The prevalence of normal DXA in the spine area was 37.85% and in the femoral neck was 52.1% [Table 3]. Hence, by simple calculation, we found that the prevalence of low bone density in the femoral neck and spine was 47.9% and 62.2%, respectively. Finally, regarding the prevalence of low bone density, there was no discernible difference between the two groups (64.8% vs. 79.9%, P = 0.081) [Table 3].

Discussion

Taking into consideration the consistent clinical

Table 2: The concentration of minerals and some hormones

Minerals and hormones	Mean±SD		*P*	Total sample (mean±SD)
	Group A	Group B		
Hgb S (g/dL)	75.6±8.49	74.39±10.89	0.508	74.94±9.85
Ca (mmol/L)	2.25±0.12	2.23±0.11	0.461	2.24±0.11
Phos (mmol/L)	1.36±0.26	1.4±0.24	0.476	1.38±0.25
Mg (mmol/L)	2.3±11.16	0.84±0.09	0.001*	1.5±7.47
ALP (U/L)	113.76±60.51	104.11±59.91	0.386	108.49±60.12
GGT (IU/L)	59.44±64.65	39.49±31.16	0.030*	48.55±50.03
Vitamin D (ng/mL)	34.82±25.37	49.48±28.54	0.004*	42.89±28.03
TSH (mIU/L)	2.01±1.32	2.2±1.45	0.470	2.12±1.39
PTH (pmol/L)	7.59±5.44	6.87±3.17	0.423	7.18±4.29

*Significant at P<0.05. *t*-test was used for all the variables in this table. Hgb S=Hemoglobin S; Ca=Calcium; Phos=Phosphate; Mg=Magnesium; ALP=Alkaline phosphate; GGT=Gamma-glutamyl transferase; TSH=Thyroid-stimulating hormone; PTH=Parathyroid hormone; SD=Standard deviation

Table 3: The prevalence of pain, scoring suggestive of osteoporosis and osteopenia by dual X-ray absorptiometry scan

	Group A, *n* (%)	Group B, *n* (%)	*P*	Total, *n* (%)
Max pain site (back)				
No	37 (68.5)	48 (73.8)	0.522	85 (71.4)
Yes	17 (31.5)	17 (26.2)		34 (28.6)
Max pain site (LL)				
No	37 (68.5)	48 (73.8)	0.522	85 (71.4)
Yes	17 (31.5)	17 (26.2)		34 (28.6)
Max pain site (General)				
No	31 (57.4)	50 (76.9)	0.023*	81 (68.1)
Yes	23 (42.6)	15 (23.1)		38 (31.9)
Femoral Dx				
T-score	−0.84 (1.82)	−0.67 (1.79)	0.509	−0.72 (1.82)
Z-score	−0.74 (1.77)	−0.59 (2.01)	0.711	−0.69 (1.78)
Normal	26 (48.1)	36 (55.4)	0.499	62 (52.1)
Spine Dx				
T-score	−1.66 (1.98)	−1.79 (2.03)	0.724	−1.73 (1.99)
Z-score	−1.52 (2.29)	−1.52 (2.00)	0.992	−1.52 (2.12)
Normal	21 (38.9)	24 (36.9)	0.816	45 (37.8)
Total prevalence of normal bone density	19 (35.1)	13 (20.1)	0.72	32 (26.9)
Total prevalence of low bone density	35 (64.8)	52 (79.9)	0.081	87 (73.1)

*Significant at $P<0.05$. The Chi-square was used for measuring maximum pain site (back, LL, and general). A t-test was used for femoral DXA, and spine DXA, and for prevalence of normal and low bone density. LL=Lower limb; Dx=DXA; DXA=Dual X-ray absorptiometry

association between bone mineral infiltration and SCD, the high rate of SCD in the Eastern Province, and the lack of research on BMD in adults with SCD, the primary objective of this research was to assess the BMD and investigate its relationship with readmission rates in $n = 119$ Saudi patients with SCD. The results showed that most of them had HgB SS or HgB SB-thalassemia with no statistical difference in genotypic distribution between the two groups. One explanation for this may be the homogeneity between the two groups, i.e., the majority of patients were Saudis with the same ethnicity and similar background, socioeconomic status, and access to health care, and no significant differences in BMI.

Evidence suggests that age, gender, and menopause were independent risk factors for low BMD in severe cases. Malnutrition and Vitamin D deficiency were strongly associated with low BMD in both SCD patients and controls.[11,27] This evidence is consistent with the results of the present study to some extent. There were no significant differences associated with severe cases, normal and/or low BMD, and demographics (i.e., age and gender). However, 25(OH) D deficiency was significantly higher in Group A compared to Group B ($P = 0.004$). At the same time, when it came to 25(OH) D levels as a measurable variable, there was no statistical difference in low BMD among Group A compared to Group B.

Malnutrition, especially 25(OH) D status, differed between groups, which may be the reason for the low BMD. Theoretically, an increase in blood cell turnover to overcome the decrease in the number of red blood cells in SCD leads to an increase in basal metabolism, which may explain 25(OH) D deficiency in Group A patients with SCD and the association between 25(OH) D, low BMD, and increased hospitalization.[11,28] Although the underlying mechanisms are still unknown, severe Vitamin D deficiency raises the risk of developing osteomyelitis and contributes to bone loss from osteoporosis caused by impaired matrix mineralization.[29-31] As a result, the most common complications leading to hospitalization in patients with SCD are painful VOCs and osteomyelitis caused by infection, dehydration, fasting, cold exposure, stress, or surgery. Moreover, since osteomyelitis is an infectious process of bone, it is a likely causative agent of painful VOC in such cases.[32,33] The results of this study showed that a higher frequency of hospital visits was associated with high levels of Mg, GGT, low levels of 25(OH) D, and general pain, thus confirming the data on lower levels of Vitamin D in SCD and its association with higher visits to the hospital and lower BMD. The pain might also be related to chronic pain associated with SCD. Many factors affect Vitamin D levels other than diet and sunlight, with strong genetic influences on circulating Vitamin D levels in different populations.[34] One explanation for such low Vitamin D levels in the Saudi population may be due to unreasonably high serum 25-hydroxyvitamin values due to different scoring methods and testing criteria, sedentary lifestyles in individuals at high risk of chronic disease, and strong genetics.[35]

Bone marrow hyperplasia, observed in SCD, is the pathogenesis of osteopenia and osteoporosis. There

are different imaging modalities to measure BMD and diagnose osteopenia and osteoporosis.[6,15,19] This study used a DXA model, and based on the *Z*-score, patients were classified as having normal or low BMD in a specific body area studied; score <−2.0: below expected range/low bone density for age; and score ≥−2: interpreted as within the expected range.[23] The prevalence of low BMD was 47.9%, of which 29.4% had osteopenia and 18.5% had osteoporosis. An earlier study by Sadat-Ali *et al*., in 2016, among n = 87 SCD patients found that more than 65% of men and 65.2% of women had either osteopenia or osteoporosis.[34] On the other hand, although earlier studies in different populations reported similar patterns, studying the prevalence and etiology of osteopenia and osteoporosis is not considered a standard treatment for SCD.[32,35,36]

The high frequency of low bone mass index in patients with SCD implies that the cause of bone loss in this population differs from that in the general population. In SCD patients, bone loss is linked to local hypoxia and decreased blood flow to the affected area, which impairs osteoclast activity and causes bone ischemia and hyperplasia of the bone marrow.[6,11,36] It was also suggested that accelerated hematopoiesis and bone loss are associated with low BMD in these patients.[36] One of the objectives of this study was to evaluate the correlation between hospitalization frequency and BMD, as it has been hypothesized that hospitalization frequency may influence BMD. However, this study did not find statistical differences in BMD between Groups A and B, making the results of DXA independent of the frequency of hospitalization. This result also challenges the previous hypothesis of skeletal ischemia and hyperplasia as an explanation for the low BMD in the SCD patient population. Moreover, this study found a contradiction in statements that patients with SCD have an increased risk of bone infarction and AVN. Thus, 16.8% of cases were complicated by AVN, all of them in the area of the hip joint, and 100% of cases had low BMD. Therefore, this research suggests that an AVN may lead to the misinterpretation of DXA scan results as low BMD, which warrants further investigation.

Limitations

In addition to the added value of this study in the literature and research on SCD, some limitations need to be acknowledged and further explored. The first limitation is the small sample size, which was included in the study due to limited knowledge about the precise effects of SCD on BMD among health-care providers and participants in the given setting. Moreover, there are no guidelines for mandatory BMD assessment in SCD in the Saudi health-care system. Thus, although low BMD has been cited as a complication of SCD, data on how high the prevalence of osteoporosis/osteopenia in patients with SCD are limited. In addition, the current study's sample size was larger than that of earlier national research aimed at gaining more insight into the effects of sickle cell anemia, patient outcomes, and the frequency of hospitalizations brought on by pain crises. Therefore, future multicenter national studies with larger sample sizes are recommended. In addition, since the results showed little difference between groups, possibly due to the homogeneity of the groups, it is recommended that future studies look at heterogenous groups, which may provide a more complete picture and/or rationalize these results. The second limitation related to some imaging during admission with active crisis, which could play a role in a DXA scan result. The third limitation is the lack of baseline DXA scan (childhood) data before this study. Despite these limitations, this study can be taken as a basis for future similar studies in different regions of the KSA.

Conclusions

This study found evidence of an association between SCD and low BMD with significantly low BMD among two-thirds of the sickle cell cases. However, there was no significant relationship between hospital admissions or disease severity with low BMD *Z*-score. The current study has shown low bone density in SCD patients with high levels of Mg, GGT, and low levels of Vitamin D (25(OH) D). Understanding the relationship between different mineral content associated with the prevalence of osteopenia and osteoporosis may help reduce the frequency of hospital visits and reduce costs and burden on patients and hospitals. Further research is required to answer the proposed debate about the accuracy of the DXA scan as diagnostic imaging in SCD patients who have reduced blood supply to the affected bone. In addition, further research is needed to investigate the need and timing of initiating osteoporosis testing in the absence of obvious fractures in this population.

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Conflicts of interest

There are no conflicts of interest.

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