International Journal of Clinical Rheumatology

Research Article

Low bone mineral density in Saudi adult patients with sickle cell disease: myth or fact?

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Objective: Although Sickle Cell Disease (SCD) is prevalent in Saudi-Arabia, there have been no data about the prevalence of low bone mineral density (BMD) in adult patients suffering from SCD in the eastern region in KSA. Our study aimed to assess the prevalence of low bone mineral density in adult patients with SCD in the eastern region in KSA and its association with other sickle cell disease manifestations.

Methodology: In King Faisal University Polyclinic, Al-Ahsa, Saudi Arabia, a cross sectional study was carried out. Ninety adult patients known to suffer from SCD between August 2017 and May 2018 were recruited for the study. Patients were interviewed; demographic and clinical data were recorded. Blood was extracted for serum levels of calcium, phosphorus, alkaline phosphatase and vitamin D 25 OH. Dual X-ray absorptiometry (DEXA) bone scan were used for all patients to determine BMD in the lumbar spine, femoral neck and distal radius. T-scores were used to classify patients as being normal, osteopenic or osteoporotic according to WHO classification. Data were analyzed by the Statistical Package for the Social Sciences (SPSS, version 20) with p value of <0.05 being statistically significant with confidence interval of 95%.

Results: A total of ninety patients were studied. There were 54 male and 36 female patients. The mean age of patients was 26.28 ± 9.37 years. Based on DEXA scan; 52/90 (57.8%) were showing low BMD defined as either osteopenic or osteoporotic. The prevalence of low BMD in our patients was highest at lumbar spine (48.1%). Low BMD was significantly correlated with low BMI (p<0.05), presence of AVN (p=0.001), low vitamin D (p=0.005).

Conclusions: This study supports the view that prevalence of osteopenia and osteoporosis among adult Saudi sickle cell anemia patients is high. As a result, sickle cell anemia is considered one of the important causes of secondary osteoporosis and physician's awareness about this issue is essential for early diagnosis of and appropriate treatment.

Keywords: DEXA • sickle cell disease • bone mineral density

Introduction

Sickle Cell Disease (SCD), one of the most widespread genetic disorders worldwide [1], is an inherited autosomal recessive disorder, characterized by the presence of pathological hemoglobin (HbS), which replaces the fetal hemoglobin to varying degrees from the age of 6 months. It is a structural hemoglobinopathy where a gene mutation of β-globin causes an increase in viscosity and adhesivity of the erythrocyte membrane, causing the typical sickle deformation of red blood cells, which tend to piling up on top of each other and are more rigid and brittle than normal [2]. Sickle cell gene is prevalent in 26% of the Saudi population; patients with homozygous sickle cells (HbSS) suffer the brunt of the chronic disease [3].

Bone involvement in patients with SCD varies from acute clinical manifestations of painful vaso-occlusive crisis to more chronic and debilitating complications, such as osteonecrosis, impaired growth, and chronic infections [4,5]. Low bone density is a systemic condition in which the reduction of bone mass and deterioration of its microarchitecture leads to increased bone fragility and susceptibility to fracture risk [6-8]. In children with SCD, investigations have documented low bone density and have postulated that poor nutrition, impaired growth hormone secretion, and delayed puberty are causal factors [5-7]. However, minimal data exist for adults [5,8]; some studies reported that adult SCD patients are more likely to be osteopenic and osteoporotic [8,9] while others claimed the reverse; in a study of 52 adult patients with sickle cell/beta-thalassemia, results showed that 57% had osteosclerosis [10], another recent study in 2018 confirmed the prevalence of high bone mineral density in sickle cell disease in 15% of SCD patients [11].

Low bone density defined as osteopenia and osteoporosis are often asymptomatic but may

cause bone pain, fractures, bone deformity, and vertebral collapse, requiring chronic analgesia and mechanical support or surgical interventions [5]. Although these bone complications may not contribute directly to increased mortality; they are a major source of co morbidity and adverse effect on patients' quality of life [12].

Despite these advances, the effect of SCD on bone mass in the literature remains poorly elucidated [13]. One study have postulated that individuals with SCD are predisposed to osteoporosis secondary to both low levels of vitamin D level and reduced bone mineral density which may lead in turn to medullary hyperplasia [14]. The pathophysiologic mechanism related to why patients with SCD have low bone mineral density and reduced vitamin D levels is not well described, though it is likely to be related to the chronic inflammation present in the bone of individuals with SCD [15]. Other studies have claimed that the pathophysiology of low bone mineral density in patients with SCD is related in part to increased bone resorption resulting from the action of inflammatory cytokines such as tumor necrosis factor–α and interleukin-6 that are released in bone during ischemic conditions [16,17]. Chronic hemolysis leads to bone marrow hyperplasia and subsequent bone deformity [5,12].

The aim of this study was to assess the prevalence of low bone mineral density in Saudi adult patients with sickle cell disease and its association with other sickle cell disease manifestations.

Patients and methods

Patients

A cross sectional study conducted on ninety adult patients with SCD were enrolled in the study. Those were outpatients of Rheumatology clinic and Internal medicine clinic at King Faisal University (KFU) Polyclinic in Al-Ahsa, Saudi Arabia. Patients were studied from August 2017 through May 2018. The study was approved by the ethical committee in King Faisal University and the study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was taken from all patients prior to entering the study.

Exclusion criteria

Patients were excluded from the study if they were below the age of twenty years or more than forty years, those who were diagnosed to have osteopenia or osteoporosis undergoing treatment, if they had hemoglobinopathy other than SCD, bone fracture, severe renal failure, or hepatic failure, pregnant females, and those under hormonal replacement therapy. Included patients were subjected to detailed history and thorough clinical examination. Each patient gave a full medical history about the frequency of chest pain, bone pain, previous hospital admissions, blood transfusions, tobacoo use, and current medications including hydroxyurea. Special emphasis was given for the presence of bone pain, history of avascular necrosis. Weight and height were recorded to calculate Body Mass Index (BMI).

Investigations

Blood was collected for haematology and biochemistry purposes. Blood sample was withdrawn for complete blood picture including reticulocytic count, first hour erythrocyte sedimentation rate (ESR, westergren), serum AST and ALT, serum creatinine and blood urea, calcium (Ca), phosphorus (Ph), total alkaline phosphatase (ALP), and vitamin D 25OH.

DEXA

BMD was measured to all our patients in the KFU polyclinic at three sites including lumbar spine, femoral neck, and distal radius using a Stratos dR, France densitometer. Patients were classified according to the World Health Organization using the T-score, which represents the number of Standard Deviations (SD) from the mean of normal subjects. Values below -2.5 at one or both sites were defined as osteoporosis. Values below -1 and above -2.5 were defined as osteopenia, and values above -1 at both sites were considered normal [18].

Statistical analysis

The results are presented as the mean ± SD. Student's unpaired t tests were used when appropriate. Frequencies were compared using the Chi-squared test or Fisher's exact test when appropriate. Pearson's correlation coefficients were calculated for continuous variables. Two-tailed values for significance were used in all statistical tests, and significance was defined as $p<0.05$. Statistical analyses were performed using SPSS statistical package, versions 20 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

90 adult Saudi SCD patients who underwent

DEXA were included. The mean age of the patients was 26.28 ± 9.37 years; there were 54 (60%) male and 36 (40%) female with the mean BMI of 16.42 ± 0.3. Thirty patients (33.3%) were treated with hydroxyurea. Clinical and laboratory characteristics of the patients are shown in Table 1. A history of femoral avascular necrosis (AVN) was reported in 31 patients (34.4%) being unilateral in 22 patients. The mean 25(OH) D serum concentration was 10 ng/mL (n=30-100 ng/ml), while the mean total calcium serum concentration was 9.5 mg/dL (8.4-10.2 mg/dl) in the whole cohort.

Bone mineral density

BMD scan in SCD patients showed normal bone density in 38/90 (42.2%) patients and 52/90 (57.8%) patients had low bone mineral density classified according to WHO criteria as osteopenia detected in 35/90 (38.9%) patients at one or more sites and as osteoporosis in 17/90 (18.9%) patients in at least at one of the three studied sites with a mean of -1.07 ± 0.65. No cases of high bone mineral density have been reported in our SCD patients. The anatomical sites of low bone mineral density in the SCD group is disclosed in Table 2, with the highest frequency at the lumbar region 25/52 (48.1%), followed by distal radius of 19/52 (36.5%) and neck of femur of 16/52 (30.8%).

Based upon the application of a chi-square test, 23 patients out of 31 having AVN at the neck of the femur found to have low BMD while the remaining 8 patients showing normal bone density and the difference was statistically significant ($p<0.005$). While for other disease characteristics including vaso-occlusive crisis, acute chest syndrome, splenomegaly; the difference was not statistically significant.

In addition, SCD patients with low BMD showed a significant decrease in body mass index and serum vitamin D levels compared to SCD patients with low bone mineral density. However, there were no significant differences in serum calcium or serum phosphorus levels between the 2 groups (Table 3).

Table 1. Demographic and clinical characteristics in SCD patients (n=90).

	Number	Frequency (%)
Gender (male/female)	54/36	60.40%
Blood transfusion	82	91.10%
Vaso-occlusive crisis	76	84.40%
Splenomegaly	39	43.30%
A vascular necrosis	31	34.40%
Use of hydroxyurea	30	33.30%
Smoking	21	23.30%
Hemolytic anemia	20	22.20%
Acute chest syndrome	11	12.20%
Septic arthritis	3	3.30%
Osteomyelitis	2	2.20%

Table 2. Percentage of patients with low bone mineral density at different bony sites (n=52)*.

Site of abnormal BMD	Abnormal BMD (n=52)
Lumbar spine	25 (48.1%)
Distal radius	19 (36.5%)
Neck of femur	16 (30.8%)
*Low BMD was diagnosed at one or more sites	

In terms of the correlation between BMD and the other studied parameters; low BMD was significantly correlated with reduction in BMI ($p<0.05$), presence of hemolytic anemia ($p<0.05$) and frequent admission to hospital ($p<0.05$). Highly significant correlation was found with the presence of AVN and low vitamin D ($p=0.001$, $p=0.005$) respectively. On the other hand, neither the presence of tobacco smoking, nor blood transfusion was associated with low BMD or with any of the other laboratory parameters (calcium, phosphorus, and alkaline phosphatase). Neither was there a significant association between low BMD and the presence of acute chest syndrome or use of hydroxurea (Table 4).

Discussion

SCD is a heterogeneous disorder, with clinical manifestations including chronic haemolysis, an increased susceptibility to infections and vaso-occlusive complications often requiring medical care [19]. Bone involvement is a frequent clinical manifestation of SCD, and it has multiple causes; however, there are few consistent clinical associations between bone mineral involvement and sickle cell disease [20]. In Addition, there is a paucity of information on BMD among adult SCD living in Saudi Arabia specifically in eastern region.

Our study included 90 Saudi adult SCD patients in Al-hasa. Diagnosis of low BMD was based on DEXA scan at lumbar spine, neck of femur, and lower radius. The aim of this study was to assess the prevalence of low bone mineral density in these patients suffering from sickle cell disease and its association with other sickle cell disease manifestations.

The prevalence of low BMD in our study was 57.8% defined as osteopenia in 38.9% and

Table 3. Comparison between normal and low BMD regarding different disease characteristics.				
	Normal BMD group (n=38)	**Low BMD group (n=52)**	**t**	**p-value**
Age	27.12 ± 8.37	26.82 ± 9.12	0.24	0.97
BMI (kg/m^2)	19.45 ± 0.3	16.24 ± 0.2	2.7	0.05*
Hb (gm/dl)	8.25 ± 0.65	8.51 ± 0.83	-0.19	0.91
Reticulocytic count (%)	5.75 ± 0.94	5.17 ± 0.90	0.23	0.86
WBCs	4834.3 ± 846.2	4987.4 ± 1528.5	-0.16	0.87
Platelets	267000 ± 17584.2	254000 ± 55741.1	0.32	0.81
AST (U/L)	35.9 ± 16	34.8 ± 12.5	0.31	0.91
ALT (U/L)	21.4 ± 15.4	20.9 ± 17.5	0.19	0.82
Urea (mg/dl)	12.3 ± 0.5	13.1 ± 1.2	-1.2	0.07
Creatinine (mg/dl)	0.64 ± 1.41	0.66 ± 1.32	-0.2	0.85
LDH (100-190 U/L)	218.89 ± 87.5	203.5 ± 56.8	0.14	0.8
Calcium (8.4-10.2 mg/dl)	9.4 ±10.1	9.1 ± 9.9	0.42	0.95
Phosphorus (2.7-4.5 mg/dl)	5.4 ± 0.7	5.9 ± 0.6	-0.17	0.82
ALP (38-126 U/L)	59 ± 87.5	65.73 ± 91.74	-0.22	0.86
Vitamin D (30-100 ng/ml)	23.15 ± 6.71	14.89 ± 4.78	3.9	0.005*
BMI: Body Mass Index; Hb: Hemoglobin; Wbcs: White Blood Cells; LDH: Lactate Dehydrogenase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase				

Table 4. Correlation between bone mineral density and different SCD characteristics.		
	Bone mineral density	
	r	**p**
Age	0.12	0.58
Gender	0.02	0.81
Smoking	0.09	0.62
Disease duration	0.04	0.87
BMI	0.44*	0.01
Acute chest syndrome	0.06	0.73
A vascular necrosis	0.27**	0.001
Frequent admissions more than 3 times per year	0.47*	0.01
Blood transfusion	-0.14	0.46
Hydroxyurea	-0.18	0.34
Hemolytic anemia	0.46*	0.01
Calcium	0.15	0.59
Phosphorus	0.09	0.61
Alkaline phosphatase	0.02	0.82
Low vitamin D	0.28**	0.005
* p<0.05 ** p<0.005		

osteoporosis in 18.9% with predilection for the lumbar spine. Little has been published about BMD in adult patients with SCD especially in the eastern region in KSA. Woods and colleagues described body composition and total body BMD and found lower BMD than expected in their 22 patients [21]. Other investigators have used quantitative computed tomography of the forearm in 32 patients with SCD and found a decrease in combined trabecular and cortical bone when compared to controls. A high prevalence of osteopenia and osteoporosis up to 70%-80% has been reported in other studies [13,22]. Another study of 32 adult patients with SCD, results found that 72% had low bone mineral density with highest detection at lumbar spine [9].

This high prevalence suggests that the etiology of bone loss in SCD differs from the general population. Bone loss in SCD is thought to be due to bone marrow hyperplasia secondary to chronic anemia, inflammation, and bone marrow ischemia [10]. Accelerated hematopoiesis and bone infarction probably contributed to the low BMD in these patients [8]. Low BMD is a hallmark of osteoporosis and increased fracture risk [23].

The present study found a strong relationship between lower BMI and lower BMD in our patients with SCD. This is in accordance with the literature [6,9]. BMI is decreased in adult SCD because of increased protein turnover

and caloric expenditure compensating for a hyperactive marrow in chronic haemolysis [24]. BMI could be affected in SCD patients since early childhood because of malnutrition, delayed growth, delayed sexual development and puberty, hormonal deficiencies as well as some specific vitamin deficiencies to which this population is more vulnerable [6,7].

Although SCD is a hemoglobin disorder, it is associated with increased incidence of bone infarctions and avascular necrosis [25]. These painful complications are one of the most important causes of morbidity in SCD; however, the basic mechanism of bone pathology in SCD has not been fully defined. In our study, AVN was reported in 31 patients (34.4%) and the majority of these patients having AVN (23 patients) found to have low BMD. In Addition, low BMD was highly correlated with the presence of AVN. Our findings come in agreement with Hassan Al-Jafar study who concluded that low BMD in SCD could be considered a risk factor contributing to the development of AVN. In their study, they hypothesized that the severity of AVN develops due to low bone mass and deterioration of the micro architecture of bone tissue [26].

Our results confirm the findings of lower level of vitamin D in SCD patients with a mean of 10 ng/mL. The low level of vitamin D in our Saudi patients with SCD was significantly correlated to the low BMD. Studies suggest that marked vitamin D deficiency also contributes to reduced bone mass due to osteomalacia resulting from impaired matrix mineralization [9,27]. However recent published data in 2018 revealed that in the Saudi Arabian population, vitamin D deficiency is as high as 60% [28]. Explanation of these lower levels of vitamin D in this population could be due to unjustified high cutoff values of serum 25 hydroxy-vitamins due to different methods of assessment and screening criteria, inactivity of the individuals specifically at risk of chronic diseases, and a strong genetic influence on the circulating vitamin D levels in Saudi Arabia population had also been reported [29]. One study in 2008 had found that administration of supplemental vitamin D to sickle patients elevated their serum levels to the normal range and lead to slight improvement in BMD, but markers of bone resorption remain unaltered suggesting abnormal bone remodeling in SCD [30].

The raised blood markers of chronic hemolysis, such LDH and reticulocyte count in our Saudi adult SCD patients; indicate high bone marrow turnover and chronic active hemolysis which may contribute to low bone mass in such patients. This is in agreement with Nouraie et al. [31] where the component of direct markers of hemolysis was higher in patients with SCD suggesting its role in low bone mass.

The use of hydroxyurea increased survival and changed the quality of life of those with recurrent vasoocclusive crises [32]. However, there is little data available regarding the impact of this treatment on the prevalence and progression of low BMD in SCD adults. In our study, the low BMD was negatively significantly correlated with the use of medication. From this point, it was suggested that its use may help to decrease the prevalence of low BMD by controlling disease activity [9].

Conclusion

Reduced bone mineral density was significantly prevalent among our studied Saudi adults of sickle cell patients in Al-Ahsa. This result could highlight the significant relevance and the need for long term comprehensive care with special attention and timely screening of BMD in SCD patients to avoid the risk of suffering consequences of low bone density. Prospective studies are needed with a larger number of patients to understand the future implications of bone densitometry changes and associated risk factors.

Conflict of interest

The Authors declare that no financial relationships and no conflict of interest concerning this manuscript.

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