

## Bone mass density in adults with sickle cell disease

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Sickle cell disease (SCD) is an inherited disorder of haemoglobin (Hb) synthesis affecting many individuals throughout the world. SCD manifests itself soon after the protective effect of HbF diminishes. Its complications are varied: acute chest syndrome, proliferative retinopathy, pulmonary hypertension, renal insufficiency, cerebral vascular accident and musculoskeletal complications. The bone involvement in SCD ranges from acute manifestations, such as painful vaso-occlusive crisis or osteomyelitis, to more chronic and debilitating complications, such as osteonecrosis, osteoporosis and osteopenia, impaired growth and chronic infections (Almeida & Roberts, 2005). Although these bone complications may not contribute directly to mortality, they are the major source of morbidity and highly impact on patients' quality of life (Almeida & Roberts, 2005). Osteopenia and osteoporosis are often asymptomatic but may cause pain, fractures, deformity and vertebral collapse requiring chronic analgesia, mechanical support and surgical interventions (Almeida & Roberts, 2005). There have been many advances in the understanding of the pathophysiology of vaso-occlusive crisis. The interaction

### Summary

Sickle cell disease (SCD) leads to many complications including osteoporosis and osteopenia. We studied the prevalence and predisposing factors of low bone mass density (BMD) in adults with SCD. In this retrospective study, dual X-ray absorptiometry bone scans were used to determine BMD in the lumbar spine, femoral neck and ultra distal radius of 103 patients (73 females, 30 males, aged 15–80 years). Chart reviews and a patient questionnaire were used to collect patient characteristics, disease course and severity, and low BMD risk factors. The 79.6% of patients (mean age  $36.5 \pm 12.5$  years) had an abnormal BMD, with a predilection for the lumbar spine ( $P = 0.001$ ). Analysis by 3 (low BMD versus very low BMD versus normal) or by 2 groups (abnormal versus normal) showed that abnormal BMD was associated with lower body mass index (BMI) ( $P = 0.003$ ), lower Hb level ( $P = 0.001$ ) and higher ferritin ( $P = 0.003$ ). Low BMD patients were more likely to be SS, SC or  $S\beta^0$ thal than  $S\beta^+$ thal ( $P = 0.022$ ). Abnormal BMD was not related to age, sex, menarche, SCD complications, number of crises, iron overload, treatment with hydroxycarbamide or desferal, renal disease, smoking or alcohol. Patients treated with hydroxycarbamide for at least 6 months were more likely to have an abnormal BMD. In this SCD population, abnormal BMD seemed to be independent of sex, age and menopause, whereas BMI, ferritin level, Hb type and level appeared to play a major role.

**Keywords:** sickle cell disease, adult, bone mass density.

of sickle red cells with endothelial cells, orchestrated by adhesion molecules, cytokines, polymorphonuclear neutrophils and platelets further clarified our understanding of the disease manifestations (Kaul & Nagel, 1993; Pathare *et al*, 2003). Despite these advances, the effect of SCD on bone mass remains poorly elucidated. Many authors agree that SCD patients are more likely to be osteopenic and osteoporotic (Brinker *et al*, 1998; Soliman *et al*, 1998; VanderJagt *et al*, 2002; Nelson *et al*, 2003; Lal *et al*, 2005; Miller *et al*, 2006; Voskaridou *et al*, 2006). The present study aimed to establish the prevalence of low bone mass in patients with SCD and examined some predisposing factors (Gutherie *et al*, 2000; Olszynski *et al*, 2004; Lamichhane, 2005; Templeton, 2005; Lane, 2006).

### Methods and population

In our Comprehensive Sickle Cell/Thalassemia Program, dual X-ray absorptiometry (DXA) is routinely performed for every patient as part of the comprehensive care. We studied 103

patients enrolled on our program, of 15 years and older (mean age  $36.4 \pm 12.5$ , range: 15–80 years), who had a DXA performed between May 1995 and December 2005. Seventy-three (70.9%) were females and 30 (29.1%) were males. The majority of the patients are of African descent. This ethnic group is believed to have average higher BMD scores than age-matched Caucasian controls (Bohannon, 1999).

The World Health Organization (WHO) defined osteopenia as a BMD value between 2.5 and 1.5 standard deviations (SD) below the young adult mean at one or more sites (T-score) and osteoporosis as 2.5 SD below this norm (Bohannon, 1999; Gutherie *et al*, 2000; Lamichhane, 2005; Lane, 2006). DXA reports from three different anatomical sites (femoral neck, lumbar spine and ultra distal region of the radius.) were used to determine the BMD. The results of DXA were initially reported using T-scores according to the WHO criteria. However, for the purpose of this study and because the age of our patients had a wide range, the term 'low BMD' was defined as a T-score between 1 and 2.5 SD below the norm, and 'very low BMD' was defined as a score of less than 2.5 SD below the norm.

Ninety-two patients had their DXA study at our main hospital. The DXA scanner used was a Hologic QDR 4500C (Waltham, MA, USA) equipped with DOS v.9.03 soft ware. The DXA used for four other patients was a GE Health Care Lunar Prodigy Advanced (Madison, WI, USA) with v.9.15 software. A further three patients had their DXA study using a GE Health Care Lunar DPX-A (Madison, WI, USA) with v.9.00 software. However, we were unable to retrieve the characteristics of the scanner for three patients.

In this retrospective study, patient charts were examined for: sex, age, body mass index ( $BMI = \text{weight (kg)}/\text{height}^2(\text{m}^2)$ ), Hb level, Hb electrophoresis, ferritin level and results of DXA. The Hb and ferritin levels were recorded, independently of the transfusion status, around the time the DXA was performed. BMI was calculated from height and weight documented at same point in time. Medications that might predispose to low BMD were noted, such as steroids, phenobarbital, phenytoin, iron chelators and treatment with hydroxycarbamide for at least 6 months before DXA. We also noted whether these patients were on calcium supplementation before DXA. As this was a retrospective study self-medication with multivitamins, over the counter medication and calcium containing preparations were not considered. Chart-documented SCD complications were recorded including: osteonecrosis, priapism, cerebrovascular accident, proliferative retinopathy, leg ulcers. Plain radiography documenting osteonecrosis before DXA was performed in response to reported painful symptoms. A history of chronic diseases that may predispose to low BMD such as renal disease, history of iron overload, malabsorption, lactose intolerance and vitamin D deficiency were investigated. Iron overload status was determined based on a history of recurrent blood transfusions and abnormal laboratory results (increased ferritin, increased transferrin, abnormal liver function tests). Patients were asked to complete a questionnaire to supplement any missing information regarding: smoking

habits, alcohol use, caffeinated beverage use and exercise. The questionnaire also discussed menarche, menopausal and perimenopausal status, history of malabsorption, lactose intolerance or vitamin D deficiency and estimated number of crises per year. Eighty-one patients responded to the questionnaire (59 females and 22 males).

The literature (Heaney, 2002) has been very controversial regarding whether a direct relationship exists between caffeine intake and osteoporosis. It mainly focused on postmenopausal osteoporosis while our population is mainly young premenopausal females. Therefore, we only focused on excessive consumption that could account for the development of low BMD. Physical activity was categorised into no exercise but some activity at home, irregular or regular exercise (walking, running, gym workout, dancing and biking). Exercising twice a week or more was considered as regular.

The recall method was used to obtain the average crises per year during the patient's lifetime. The obtained data was compared with hospital records (hospital admissions, emergency room visits, transfusions). These two methods matched closely for long-term follow-up patients. All data were collected in reference to the end point, which was the date DXA was performed. Our institution internal review board approved the study. No consents were required as the DXA were part of the comprehensive care the patients received whilst attending the program.

### Statistical analysis

Patients were divided into three groups (low BMD, very low BMD and normal) or two groups (normal *versus* abnormal). Analysis throughout the study was conducted using a three-group model as well as a two-group model. Throughout the study an alpha level of 0.05 was set. The distribution of most of the numerical data was normal, except ferritin, which required log transformation prior to testing. The ferritin levels were skewed to the right, possibly reflecting the transfusion history of many of our patients.

Analysis of variance (ANOVA) was applied for numerical variables to evaluate the differences between the groups. Pearson chi-squared analyses were used for categorical variables. *Post hoc* test was performed when appropriate. A step-wise logistic regression analysis was conducted. For the purpose of testing the anatomical site, 82 patients with abnormal BMD were studied to ascertain, if the rate at which each of three anatomic locations differed. As the disease can be in multiple sites, the status of each of the three sites was tested for each patient. A repeated-measures multivariate analysis of variance (MANOVA) was deemed to be the appropriate and the most powerful test. A *post hoc* pair comparison was also performed.

### Results

A prevalence of 79.6% was found for low BMD. Three groups of patients were observed: low BMD ( $n = 45, 43.7\%$ ); very low

**Table 1.** Patient's characteristics and haematological parameters.

	Low BMD mean $\pm$ SD	Very low BMD mean $\pm$ SD	Normal mean $\pm$ SD	P-value (3 groups)	P-value (2 groups)
Age (years) ( $n = 103$ )	35.2 $\pm$ 9.9	37 $\pm$ 15	35.9 $\pm$ 11	0.628 NS	0.822 NS
Sex ( $n = 103$ )	F 39.7% ( $n = 29$ ) M 26.7% ( $n = 8$ )	F 42.5% ( $n = 31$ ) M 46.7% ( $n = 14$ )	F 17.8% ( $n = 13$ ) M 26.7% ( $n = 8$ )	0.384 NS	0.311 NS
BMI(kg/m <sup>2</sup> ) ( $n = 103$ )	24 $\pm$ 5	21.9 $\pm$ 5	27.1 $\pm$ 7.3	0.003 S	0.003 S
Hb(g/l) ( $n = 103$ )	91.2 $\pm$ 18	89 $\pm$ 18	108 $\pm$ 19	0.001 S	<0.0001 S
Electrophoresis ( $n = 103$ )					
SS ( $n = 60$ )	36.7% ( $n = 22$ )	50% ( $n = 30$ )	13.3% ( $n = 8$ )	0.022 S	0.018 S
SC ( $n = 25$ )	48% ( $n = 12$ )	32% ( $n = 8$ )	20% ( $n = 5$ )		
S $\beta^+$ thal ( $n = 11$ )	0% ( $n = 0$ )	45.5% ( $n = 5$ )	54.5% ( $n = 6$ )		
S $\beta^0$ thal ( $n = 7$ )	42.9% ( $n = 3$ )	28.6% ( $n = 2$ )	28.6% ( $n = 2$ )		
Ferritin without outlier ( $\mu$ g/l) ( $n = 82$ )	994.2 $\pm$ 1712.4	1406.5 $\pm$ 2430.8	356.6 $\pm$ 648.9	0.003 S	0.011 S
Age at menarche, years ( $n = 61$ )	14.6 $\pm$ 1.6	14.5 $\pm$ 2.8	13.6 $\pm$ 2	0.446 NS	0.210 NS

BMD, bone mass density; S, significant; NS, non-significant, F, female; M, male;  $n$ , number of patients.

2-group: characteristics of patients with abnormal BMD *versus* normal BMD are compared. 3-group: characteristics of patients very low BMD *versus* low BMD *versus* normal BMD are compared.

Percentages are given for categorical variables.

BMD ( $n = 37$ , 35.9%) and normal ( $n = 21$ , 20.4%). There was no significant difference between these groups in sex or age, regardless of the model used for statistical analysis (Table 1). There was a significant difference in the involvement of the lumbar spine compared with the femoral neck and ultra distal region of the radius (Pillai's trace = 40.42,  $P < 0.001$ ). There was no significant difference between the radius and femoral neck. The likelihood of having an abnormal BMD in the lumbar spine was significantly higher than in any other site. The BMI ranged between 15.4 and 51.4 with a mean of 23.7  $\pm$  5.8. There was a high level of significance between the groups regardless of the model used for statistical analysis. The higher the BMI, the lesser was the likelihood of developing low BMD (Table 1, Fig 1).

The haemoglobin level ranged from 59 to 142 g/l, with a mean of 94  $\pm$  19.5 g/l. The inverse relationship of Hb and BMD was highly significant, regardless of the model used for statistical analysis. The lower the Hb, the more likely a patient would develop abnormal BMD. There was a significant influence of the Hb type on the outcome, which resulted from the differences between the S $\beta^+$ thal group and all the other groups (SS, SC, S $\beta^0$ thal). The percentage of S $\beta^+$ thal with normal BMD was significantly higher, indicating that S $\beta^+$ thal patients were more likely to have normal BMD (Table 1; Figure 1).

The Hb level in the S $\beta^+$ thal group was significantly higher than SS ( $P < 0.0001$ ) and S $\beta^0$ thal ( $P = 0.002$ ) but not SC ( $P = 1.0$ ) groups. High Hb levels in the S $\beta^+$ thal group could explain their decreased rates of low BMD. The SC group was not found to have reduced rates of lower BMD, despite the relatively higher mean Hb level (Table 2). For the three-category and then for the two-category renditions of low BMD, a chi-squared test of independence was conducted to assess the

relationship between the type of haemoglobinopathy and low BMD. In both models, the chi-square was significant indicating that there was evidence of a relationship between the electrophoretic profile and low BMD.

The ferritin levels were obtained in 83 patients (range, 1010243.4  $\mu$ g/l, with an outlier of 412 003  $\mu$ g/l). After removal of the outlier, a high level of significance was obtained, indicating that a higher ferritin level increases the risk of developing low BMD despite the model used for statistical analysis (Table 1). We examined the likelihood of developing low BMD once patients had at least one SCD complication. There was no significant difference between the groups regardless of the type of statistical analysis. The relationship became significant ( $P = 0.048$ ) in the two-group model when only osteonecrosis was considered as a SCD complication. However, the relationship was not significant in the three-group model with  $P = 0.054$  (Table 2).

Fifty-five patients had an average of three crises or more a year, 47 others did not. No significant relationship was found between the number of crisis and the likelihood of developing low BMD. Sixteen (15.5%) patients were reported to be iron overloaded; six had low BMD, nine had very low BMD and one had normal DXA. Chi-Squared (0.28) and Fisher's exact test (0.313) were not significant for these findings (three-group analysis). A two-group model chi-square (0.127) was also not significant. Six of our patients had end stage renal disease, of which four had very low BMD and two had low BMD. Chi-Squared (0.35) as well as Fisher's exact test (0.416) did not show any significant relationship between this diagnosis and BMD (three-group analysis). The two-group analysis gave a  $P$ -value of 0.2.

The chart review confirmed the diagnosis of lactose intolerance in one patient who was on a lactose-free diet.

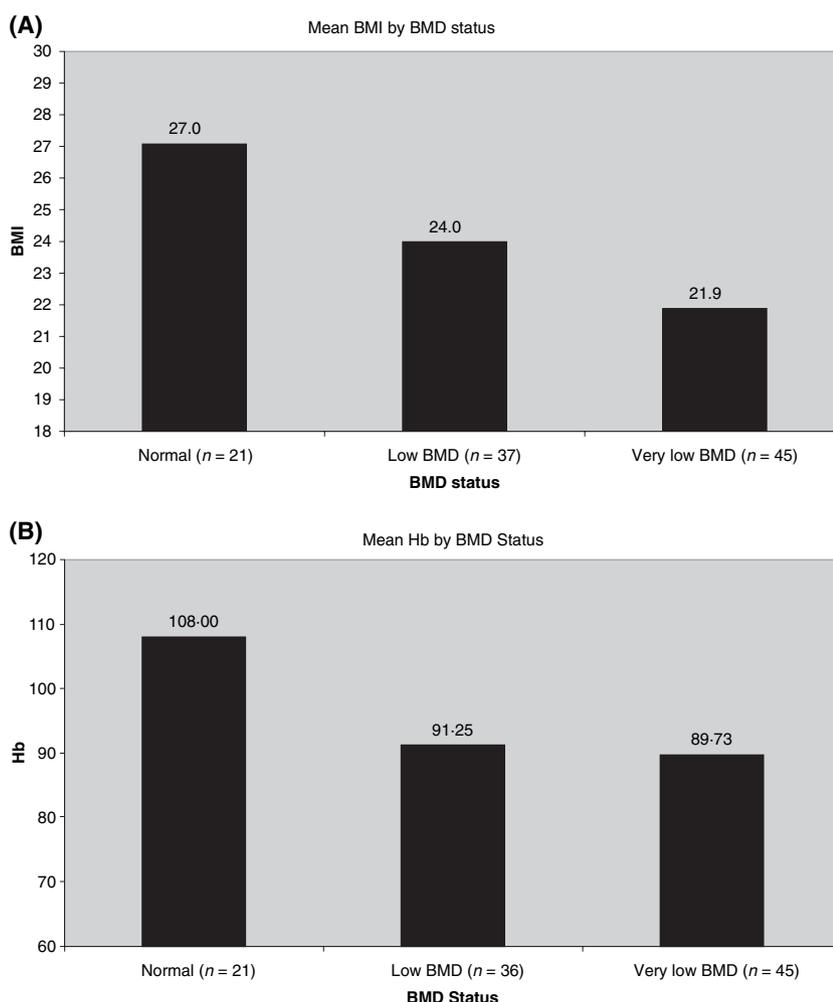


Fig 1. (A) Mean bone mass density (BMI) (kg/m<sup>2</sup>) by BMD status ( $P = 0.003$ ). Columns are compared with each other. (B) Mean Hb (g/l) by BMD status ( $P = 0.001$ ). Columns are compared with each other.

Table 2. Hb level (g/l) by Hb electrophoretic profile.

Genotype	Mean Hb $\pm$ SD (g/l)	Range
SS	85 $\pm$ 15	59–122
SC	108 $\pm$ 16	69–139
S $\beta^+$ thal	116 $\pm$ 16	91–142
S $\beta^0$ thal	88 $\pm$ 15	72–113

SD, standard deviation.

When responding to the questionnaire, 21 other patients either claimed to have lactose intolerance or symptoms of lactose intolerance. On further questioning, two patients claimed a history of chronic malabsorptive symptoms. Five patients had been told, in other institutions, they had vitamin D deficiency. When asked about dairy intake, 29 patients denied any use of dairy product for various reasons and 52 acknowledged the consumption of some dairy products. These data were not included in the analysis because of their qualitative nature and inaccuracy.

Fifteen patients were on hydroxycarbamide while 88 were not. Hydroxycarbamide use was significant in the two-group model ( $P = 0.037$ ), but not in the three-group model (chi-squared test,  $P = 0.078$ ; Fisher exact test,  $P = 0.059$ ) (Table 3). Only one patient was on steroid treatment before DXA. Four patients were on phenytoin, two on iron chelators and none was on phenobarbital. Eight were on calcium acetate before DXA because of renal disease. These numbers were too few for statistical comparison. In females, we investigated risk factors for low BMD. The age at menarche ranged between 9 and 21 years old with a mean of  $14.4 \pm 2.25$  years. Even though females with abnormal BMD reached menarche later than females with normal BMD, there was no significant difference between groups (Table 1). We report 13 postmenopausal patients and an additional two who had bilateral oophorectomy before DXA. We did not have available data on menopause for seven patients. Five patients reported perimenopausal symptoms and 11 reported irregular menstruation (because of ovarian cysts, contraception, overweight and other reasons) before DXA. The chart review did not disclose a

**Table 3.** Some risk factors of low bone mass density (BMD) in sickle cell disease (SCD) patients.

	Low BMD mean $\pm$ SD	Very low BMD mean $\pm$ SD	Normal mean $\pm$ SD	P-value (3 groups)	P-value (2 groups)
Osteonecrosis ( $n = 103$ )	15.5% ( $n = 16$ )	11.7% ( $n = 12$ )	11.7% ( $n = 12$ )	0.048 S	0.054 NS
Hydroxycarbamide(+) ( $n = 15$ )	53.3% ( $n = 8$ )	46.7% ( $n = 7$ )	0%	0.078 NS	0.037 S
Smoking ( $n = 90$ )					
Never $n = 72$	38.9% ( $n = 28$ )	47.2% ( $n = 34$ )	13.9% ( $n = 10$ )	0.534 NS	0.225 NS
Given up $n = 8$	37.5% ( $n = 3$ )	25% ( $n = 2$ )	37.5% ( $n = 3$ )		
Current $n = 10$	40% ( $n = 4$ )	40% ( $n = 4$ )	20% ( $n = 2$ )		
Alcohol ( $n = 89$ )					
Never $n = 46$	47.8% ( $n = 22$ )	37% ( $n = 17$ )	15.2 ( $n = 7$ )	0.299 NS	0.637 NS
Occasional $n = 39$	28.2% ( $n = 11$ )	53.8% ( $n = 21$ )	17.9% ( $n = 7$ )		
Regular $n = 4$	25% ( $n = 1$ )	75% ( $n = 3$ )	0% ( $n = 0$ )		
Exercise ( $n = 83$ )					
None $n = 30$	35.5% ( $n = 11$ )	45.9% ( $n = 17$ )	13.3% ( $n = 2$ )	0.055 NS	0.092 NS
Irregular $n = 20$	12.9 ( $n = 4$ )	27% ( $n = 10$ )	40% ( $n = 6$ )		
Regular $n = 33$	51.6 ( $n = 16$ )	27% ( $n = 10$ )	46.7% ( $n = 7$ )		

NS, non-significant;  $n$ , number of patients.

2-group: Characteristics of patients with abnormal BMD *versus* normal BMD are compared.

3-group: Characteristics of patients very low BMD *versus* low BMD *versus* normal BMD are compared.

history of hypogonadism in any of our patients. None of the following factors was found to be significant: alcohol use, smoking and exercise (Table 2). Only five patients reported the habit of ingesting more than five caffeinated beverages per day (>150 mg of caffeine daily).

Binary logistic regression analysis was conducted (two-group model). The results of this analysis indicated that the likelihood of developing abnormal BMD increases with low BMI, low Hb level, smoking and female gender (patients who smoke had more risk of developing abnormal BMD compared with those that had given up smoking and non-smokers). Based on the Wald statistic and significance level ( $P$ -value), Hb level appeared to be the strongest predictor of abnormal BMD.

Multinomial logistic regression analysis was also conducted (three-group model), with normal patients representing the reference (baseline) category. The results of this analysis showed that the likelihood of developing abnormal BMD (low or very low BMD) increased with decreasing Hb level, decreasing BMI and aging. Based on the Wald statistic and significance level ( $P$ -value), Hb level was the strongest and the sole predictor of low BMD. Hb level, BMI, age and an interaction term involving age and BMI were all instrumental in predicting very low BMD. The decrease in probability of very low BMD (*versus* normal) that occurred with increasing BMI and age, progressively decreased per unit increase in BMI and age at higher values of age and BMI.

## Discussion

The present study found a high prevalence (79.6%) of abnormal BMD (low and very low) by DXA in SCD adults, with predilection for the lumbar spine. Other investigators

(Brinker *et al*, 1998; Nelson *et al*, 2003; Miller *et al*, 2006) using DXA and quantitative computerized tomography, respectively, reported similar prevalence rates in young SCD adults. Our patients were mainly young black females. In our series and in others, there was no significant relationship between older age and BMD (Voskaridou *et al*, 2006). Our SCD patients seemed to develop abnormal BMD shortly after the normal population acquires peak bone mass (Lamichhane, 2005). This observation of young adults with abnormal BMD could simply be the result and continuum of what is seen in SCD children and adolescents (Brinker *et al*, 1998; Soliman *et al*, 1998; VanderJagt *et al*, 2002; Lal *et al*, 2005). In fact, SCD youngsters fail to attain optimal peak bone mass during growth (Soliman *et al*, 1998; VanderJagt *et al*, 2002), which puts them at high risk of developing an abnormal BMD later in life if no intervention is implemented.

In our population, no significant difference was found between males and females. Nevertheless, when regression analysis was conducted, the female gender was one predictive factor in developing abnormal BMD. In addition, female children and adolescents with SCD showed some bone differences when compared with their male counterparts (VanderJagt *et al*, 2002). One of these differences was the significant correlation between the biochemical markers of bone turnover and the bone ultrasound analysis in females, whereas there was none in males (VanderJagt *et al*, 2002).

We observed a significant relationship between lower Hb levels and lower BMD. In fact, low Hb level was the strongest predictor of abnormal BMD. Chronic and severe anaemia places a burden on the bone marrow, with increased erythropoiesis causing hyperplasia of the bone marrow, a decrease in the trabecular network and osteopenia (Brinker *et al*, 1998) and bone destruction (Voskaridou *et al*, 2006). Some studies,

however, (Brinker *et al*, 1998; Miller *et al*, 2006) did not find any correlation between Hb level and BMD values.

We observed a significant difference between S $\beta^+$ thal and all other genotypes (SS, SC, S $\beta^0$ thal). S $\beta^+$ thal patients have a low prevalence of low BMD when compared with the other groups. Roughly similar percentages, found in Greece (Voskaridou *et al*, 2006), confirm our findings. Our larger sample could explain these findings when compared with recent studies conducted in the USA (Miller *et al*, 2006). Because Hb level was the strongest predictor of low BMD in our study; the significantly higher Hb levels in S $\beta^+$ thal patients could explain the low prevalence of low BMD in this group.

In accordance with the literature (Soliman *et al*, 1998; Miller *et al*, 2006), the present study found a strong relationship between lower BMI and lower BMD in young SCD adults. A study of risk factor for decreased BMD in premenopausal women showed the significant influence of low BMI (Krahe *et al*, 1997). BMI is decreased in adult SCD because of increased protein turnover and caloric expenditure compensating for a hyperactive marrow in chronic haemolysis (Borrel *et al*, 1998). BMI, weight and therefore BMD could be affected in SCD patients since early childhood because of malnutrition, delayed growth, delayed sexual development and puberty, hormonal deficiencies (insulin-like growth factor 1, insulin-like growth factor binding protein 3) as well as some specific vitamin deficiencies to which this population is more vulnerable (Soliman *et al*, 1998; VanderJagt *et al*, 2002). Some studies stated that, in the malnourished state of children with SCD, weight may be more important than age in the acquisition of bone mass (Soliman *et al*, 1998; VanderJagt *et al*, 2002). Other studies (Woods *et al*, 2001) reported low BMD in young premenopausal SCD females (mean age  $30.5 \pm 9.3$  years) with normal weight and 'acceptable' BMI. They postulated that these females have lower energy expenditure compared with children and adolescents with SCD and have a higher body fat.

We found a significant relationship between high ferritin level and abnormal BMD. Studies involving SCD children did not show any relationship between ferritin and BMD (Soliman *et al*, 1998). Ferritin levels may increase with age and reflect variables not yet present in children including: siderosis, multiple transfusions, inflammation and/or infection. Soliman *et al* (1998) even incriminated the detrimental effects of excess circulating iron on calcium deposition in bone.

Some investigators (Soliman *et al*, 1998) implicated osteonecrosis as a factor for abnormal BMD. As the significance in our study depends on the model used for statistical analysis, we refer to some difficulties interpreting DXA. DXA may not be the ideal test reporting the precise BMD in patients with osteonecrosis. Bones affected by infarction stimulate new bone formation, osteolysis, and sclerosis, leading to focal areas of increased BMD (Brinker *et al*, 1998; Nelson *et al*, 2003; Voskaridou *et al*, 2006). This is particularly true when osteonecrosis occurs at the studied anatomic areas. The overall SCD effect on BMD in the presence of osteonecrosis, and

hence osteosclerosis, is believed by some to be decreased (Brinker *et al*, 1998; Nelson *et al*, 2003) and to be increased by others (Voskaridou *et al*, 2006).

Calcium is a major factor in determining BMD from an early age (Krahe *et al*, 1997; Lal *et al*, 2005). Lal *et al* (2005) found that children with sickle cell anaemia have a low calcium intake. Some investigators demonstrated that the 25-hydroxy-vitamin D levels were low in SCD children and young adults diagnosed with low BMD (Lal *et al*, 2005; Miller *et al*, 2006). Furthermore, osteomalacia presents as low BMD on DXA and measuring the level of vitamin D will help differentiate low BMD from osteomalacia. SCD patients were even reported to have more specific vitamin and oligoelement deficiencies (magnesium, zinc) owing to decreased intake during vaso-occlusive crises (Miller *et al*, 2006). In light of the previous studies, research should be dedicated to calcium, vitamin D and oligoelement intake and metabolism in all SCD patients, with a nutritional quantitative evaluation of these necessary nutrients.

The use of hydroxycarbamide increased survival and changed the quality of life of those with recurrent vaso-occlusive crises (Steinberg, 2002). However, there is little data available regarding the impact of this treatment on the prevalence and progression of abnormal BMD in SCD adults. In our study, the significance of hydroxycarbamide as a factor influencing BMD depended on the model used for statistical analysis. Hydroxycarbamide use seemed to decrease the prevalence of abnormal BMD. The impact of hydroxycarbamide on BMD is nevertheless controversial (Miller *et al*, 2006).

With regard to painful crisis, other studies and this study did not seem to find any relationship between the number of crises and abnormal BMD (Miller *et al*, 2006; Voskaridou *et al*, 2006). The delay of sexual development in females with SCD is widely recognised (Serjeant *et al*, 2001). The present study confirmed this delay. In our study, females with abnormal BMD presented with delayed menarche compared with normal subjects. However, there was no significant difference between the groups. Inaccuracy in recollecting the age at menarche could explain our results. Low BMD in SCD patients seems to be multifactorial and definitely independent of age, menarche or menopausal status.

In our study, selection bias could not be excluded. Indeed, not every patient enrolled in our programme complied with the DXA study. Socioeconomic aspects, disease severity, health status awareness as well as educational factors could have contributed to our findings. Not every patient enrolled in the study answered the questionnaire. Patients with more severe disease could be less willing to answer a questionnaire; the opposite could also be true. Further studies that include larger, more homogenous (equal number of males and females) and more compliant populations are needed. Because the life expectancy of SCD patients has improved since the implementation of comprehensive sickle cell care, there is a desire to emphasise long-term health maintenance in these patients. Osteoporosis may be one of the major

public health problems in SCD patients, particularly if it starts at an early age.

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