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Does high serum iron level induce low bone mass in sickle cell anemia?

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Abstract Iron overload is quite common in patients suffering from hemoglobinopathies causing arthropathies, endocrinal affection and neuropathies. Recently low bone mass was added to the list of complications. This study is conducted to find any correlation between serum iron level and low bone mass in sickle cell anemia (SCA). Patients ≥18 years of age with sickle cell anemia, who attended outpatient clinics or admitted to King Fahd University Hospital, Al Khobar, Saudi Arabia,between 1st September 2006 and August 2007 were the subjects of this study. Patients age and sex were documented and body mass index was calculated. Apart from routine hematological tests, serum ferritin, serum Iron level, total estradiol, testosterone level was done. Bone mineral density measurement was done using dual energy X-ray absorptiometry (DEXA) at upper femur and lumbar spine. The data of 100 patients was analyzed, 48 males and 52 females. The mean age was 27.5 ± 6.1 years. In 64 patients (32 males and 32 females) serum iron level was 319.35 μg/dl and the mean serum ferritin level in males and females was within the normal range. Sixty-eight percent of females and 71.8% of males patients in whom serum iron was high had lower bone mass $P = < 0.001$. Our study shows that SCA patients in whom serum iron level was higher than normal effected bone mass. Further studies are needed to confirm this as a cause of osteoporosis in SCA patients.

Keywords Low bone mass · Serum iron level · Sickle cell anemia · Osteoporosis

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Introduction

Sickle cell anemia (SCA) is an inherited hemoglobin synthesis disorder, with chronic hemolysis requiring repeated blood transfusions. Multiple transfusions do save lives but has complications of its own and Iron overload is one of them. The prevalence of iron overload in sickle cell disease (Banerjee et al. 2001; Harmatz et al. 2000) and thalassemia with associated endocrinopathy was recently reported (Al-Elq and Al-Saeed 2004; Fung et al. 2006). Reports indicate that patients with iron overload have an increased risk

of arthropathies, neuro-degenerative affection and malignancies Weinberg (2007). Low bone mass due to sickle cell disease was recently recognized (Miller et al. 2006; Sadat-Ali and AlElq 2007; Sarrai et al. 2007). Diamond, Stiel and Posen (1989) reported hypogonadism as the cause of osteoporosis in hemochromatosis but Eyres et al. (1992) suggested that factors other than hypogonadism contribute to osteoporosis. Sickle cell anemia is common among ethnic Saudi Arabian population but there is little literature on effect of serum iron level, iron overload and osteoporosis. We wish to report an observation of high level of serum iron levels in SCA patients and its effect of bone mass.

Patients and methods

A cross-sectional study was conducted on patients with sickle cell anemia (SCA) who attended outpatients clinics to King Fahd University Hospital, Al Khobar, Saudi Arabia, between 1st September 2006 and August 2007. A verbal consent was obtained to participate in the study. Patient's age, sex, number of blood transfusions was documented and body mass index (BMI) was calculated. Blood was drawn for complete blood picture, hemoglobin electrophoresis, other tests done were renal function test (RFT), liver function test (LFT), calcium, phosphorus, alkaline phosphatase, serum ferritin level, serum Iron level, total estradiol (E2) and total testosterone (Te). Patients with <18 years and more than 35 years and other hemoglobinopathies were excluded from the analysis. Bone mineral density (BMD) was measured using DEXA scan, Hologic Inc. at the hip region and lumbar spine (L1–L4 spine). Osteopenia and osteoporosis was defined as per the WHO criteria. The data was entered in the data base and analyzed using SPSS (Statistical package for the social sciences), Chicago, Illinois. Means were compared using Student's "*t*" test and χ^2 as needed and a *P* value of <0.05 was considered significant at 95%.

Confidence interval (CI)

The study was approved by the Ethics and Research Committee of the College of Medicine, King Faisal University, Dammam and King Fahd University Hospital, AlKhobar.

Results

The data of 100 patients was analyzed 48 were males and 52 females. The mean age was 27.5 ± 6.1 years. Thirty-two (66.6%) of male patients had serum iron level higher than normal, and serum ferritin level was within normal range in both the normal and in iron overload group 75.3 ng/dl and 68.2 ng/dl (normal range 6–282 ng/dl) (Table 1). Twenty-three (71.8%) of the males in the iron overload group had low bone mass. Bone mineral density in the iron overload group was lower 0.782 g/cm^2 versus 0.910 g/cm^2 ($P = 0.01$). Serum estradiol and testosterone levels were within the normal range. Twenty-two (68%) of

Table 1 Data of male sickle cell anemia patients

Parameter	Normal serum iron level	Abnormal serum iron level	*P* Value
Number of patients	16	32	
Patients with low bone mass	7 (43.7%)	23 (71.8%)	0.09
Age years	26.1 ± 7.1	28 ± 7.5	0.3
Hb Concentration grams/l	9.5 ± 0.9 (8.4–11.1)	9.1 ± 0.91 (8.4–10.1)	
Number of blood transfusions	2.1 (0–4)	4.6 (0–10)	0.8
Serum ferritin level (6–282 ng/dl)	75.3 ± 36.2	68.2 ± 42.4	0.5
Serum iron level (40–135 μg/dl)	102.2 ± 19.27	317.7 ± 220.5	0.001
Testosterone level >50 ng/dl	485.8 ± 114	401.3 ± 118	0.2
Estradiol level 11–44 pg/ml	29 ± 6.19	23 ± 5.48	0.002
BMD g/cm^2	0.910 ± 0.34	0.782 ± 0.22	0.01
T score	−1.1 ± 1.2	−1.7 ± 2.0	
Z score	−1.0 ± 1.8	−1.4 ± 1.9	

Table 2 Data of female patients sickle cell anemia

Parameter	Normal serum iron level	Abnormal serum iron level	*P* Value
Number of patients	20	32	
Patients with low bone mass	7 (35%)	22 (68%)	0.01
Age (Years)	26 ± 2.7	30 ± 4.2	0.001
Hb Concentration gram/dl	9.725 ± 0.97 (8.7–11.7)	9.43 ± 0.97 (7.9–10.3)	
Number of blood transfusions	4 (0–6)	5.4 (0–10)	0.5
Serum ferritin level (6–282 ng/dl)	65.8 ± 22.9	60 ± 16.8	0.3
Serum iron level (40–135 μg/dl)	68.34 ± 59.2	321 ± 124	0.001
Testosterone level >50 ng/dl	113.2 ± 138.8	129 ± 174.9	0.7
Estradiol level 11–44 pg/ml	57.5 ± 36.5	32.2 ± 34.5	0.01
BMD g/cm^2	0.91 ± 0.21	0.72 ± 0.14	0.05
T score	−1.6 ± 2.1	−2.2 ± 1.5	
Z score	−1.5 ± 2.1	−1.8 ± 1.5	

the female patients in whom serum iron level was mean of 321 μg/dl suffered low bone mass and in 20 patients the serum iron level was 68.34 μg/dl with normal bone mass ($P = 0.001$). Serum ferritin level in both groups was in normal range 65.8 and 60 ng/dl (normal range 6–282 ng/dl) (Table 2). Bone mineral density in patients with high serum level was 0.720 g/cm^2 versus 0.910 g/cm^2 ($P = 0.05$). In males the average transfusion was 2.1 times (0–4) in the normal serum iron level whereas in the abnormal serum iron group the average blood transfusion was 4.6 times (0–10). In the females the number of transfusion was 4 and 5.4 times respectively.

Discussion

The results of this study show that in 64% of patients suffering with sickle cell anemia had abnormally high serum iron levels and secondly 70% of patients with sickle cell anemia had low bone mass (osteopenia and osteoporosis). Increased morbidity and mortality due to iron overload was observed in patients with hemochromatosis and β thalassemia (Brittenham et al. 1994; Niederau et al. 1996). Recent data even though limited suggests that in patients with SCA, Iron overload occurs (Ballas 2001; Manci et al. 2003, and Vichinsky et al. 2005), with a mortality of 7% directly related to iron overload Darbari et al. (2006). In this study we found that in 64% of the SCA patients, serum iron levels was significantly higher with normal serum ferritin levels. In our male patients there was no significant difference of average blood transfusions between normal and abnormal serum iron levels (2.1–4.6), and in the female patients the results were similar (4–5.4).

Al-Rimawi et al. (2005) found that in their patients of beta –thalassemia, iron overload was reported to be the cause of abnormal endocrine function and in our patients estradiol levels was significantly lower in patients with abnormal serum iron levels.

In the past few years researches had focused injury to the skeletal tissues due to iron overload. Eyres et al. (1992) first reported osteoporotic related fractures due to hemochromatosis in an eugonadal patient. This report gave a cue that iron overload may induce osteoporosis. Guggenbuhl and his associates (2005) found that in untreated hemochromatosis patients 78.9% of them had osteopenia and 34.2% osteoporosis, with normal vitamin D and parathyroid hormone levels. Osteoporosis due to iron overload in β thalassemia patients was reported in over 65% Chan et al. (2002) and Vogiatzi et al. 2004). Shah et al. (2004) found that in sickle cell anemia patients, the prevalence of iron overload and osteoporosis was 47% and in our patients the prevalence of osteopenia and osteoporosis was 70%.

The cause or causes of low bone mass due to iron overload is still being investigated. Matsushima et al. (2003) found in experimental animals raised iron level suppressed bone remodeling, while Voskaridou and Terpos (2004) implicated diminished osteoblastic

function and increased osteoclastic activity. Recently Weinberg (2007) concluded that in iron over load patients osteoporosis is caused due to suppression of osteoblast formation. We believe that not only iron overload but raised serum iron levels does play a role in the cause of osteopenia and osteoporosis.

Our study has few limitations. All the diagnostic parameters for iron overload were not performed. Secondly we have taken only serum iron level and serum ferritin level, total estradiol and testosterone levels for our analysis. In conclusion our study confirms that in patients with SCA, even high serum iron levels with normal serum ferritin level induces low bone mass. Osteoporosis due to high serum iron and iron overload in SCA still remains the most under investigated issue hence more studies are needed to formulate consensus for early diagnosis and appropriate management.

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