Relation between bone mineral density and serum ferritin levels in patients with thalassemia major

Original Article

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Abstract:

Background: Thalassemia/haemoglobinopathy is a hereditary disease with increased erythropoiesis and expansion of the bone marrow cavity. Consequently, there is a reduction in trabecular bone tissue resulting in osteopenia/osteoporosis. The present study was performed to determine bone mineral density (BMD) in children and adolescents with major thalassemia and its correlation with serum ferritin level.

Methods: Seventy children and adolescents with major thalassemia were divided into two groups, (each group with 35 patients). Patients with serum ferritin level more than 1500 ng/dl were defined as case group and those with serum ferritin level lower than 1500 ng/dl were defined as control group. Thyroid and parathyroid function tests were performed as well as calcium and phosphorus serum level were checked. Dual X-ray Absorptiometry (DXA) was the diagnostic test for osteoporosis. Only patients with transfusion-dependent thalassemia major were enrolled. Patients with delayed puberty, hypothyroidism or parathyroid dysfunction, renal failure, liver failure, growth hormone deficiency and also those who used Calcitriol were excluded from the research.

Results: Results showed that the mean serum ferritin in patients who had femoral osteoporosis was higher from those with osteopenia and normal density in the femur. (p=0.001). In addition, the mean serum ferritin in patients with vertebral osteoporosis was higher than that in those with osteopenia and normal bone density in the vertebral bones, (p=0.002). There is a significant difference between serum ferritin in different bone densities.

Conclusions: Bone density is a good indicator of bone status in patients with major thalassemia and we recommend measuring it annually.

Keywords: beta-Thalassemia Major, Absorptiometry-Photon, Bone Density, Osteoporosis, Ferritin

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Introduction:

Thalassemia is a hereditary disease that causes imbalanced production of globin chains. This disorder causes inefficient erythropoiesis as well as increased peripheral hemolysis. Because of the increased inefficient erythropoiesis, the bone marrow cavity becomes larger, and cortical and tubular parts of the bone tissue will decrease [1, 2]. Thus, thalassemia patients will develop multiple bone disorders including bone pain, bone deformities, delayed bone growth, growth retardation, rickets disease, scoliosis, spinal deformities, pathological fractures, osteopenia and osteoporosis [3, 4]. Osteoporosis is defined as bone tissue loss and degradation of the bone skeleton, which leads to reduced bone strength and increased risk of bone fractures [5].

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Bone mineral density (BMD) is a good indicator for assessment of bone status and the most important predictor of childhood thalassemia [6], which can be fatal. However, treatment with blood transfusions can play a crucial role in reducing mortality and morbidities as well as enhancing the quality of life and increased longevity of these patients [7].

However, with aging the problem of osteoporosis is the main causes of disability. Besides the aforementioned issues, it should be noted that blood transfusion therapy leads to significant side effects. One of the most important complications is iron overload [8].

The major complications caused by iron overload including hypogonadism, hyperparathyroidism, diabetes mellitus, hypothyroidism and cardiomyopathies. Chelation therapy can be used to mitigate above iron overload induced complications [9].

Ferritin is an iron storage form in the body, which releases the required iron when needed. All thalassemia patients using iron chelators should be monitored and evaluated regarding serum ferritin levels [10].

Usually β-Thalassemia major patients will be diagnosed at the first years of life. After that, patients underwent regular blood transfusion. One year after regular blood transfusion, iron chelator had been started. Iron deposition may induce bone damage like as osteopenia and osteoporosis. The purpose of this study was to evaluate the bone density of femoral and vertebral column through DUAL ENERGY X RAY ABSORPTIOMETRY (DEXA) method in thalassemia major patients in age range of 15 to 45 years old and its relationship with serum ferritin levels.

Methods:

This case-control study was conducted on 70 patients with thalassemia major between 15 and 45 years old. The studied subjects were thalassemia patients referred to the Thalassemia Center in Amirkola hospital in 2012-2014. The patients were divided into two groups (case and control) based on serum ferritin levels. There were 35 subjects in each group. The two groups were matched regarding age and gender. The study inclusion criterion was merely the patients with thalassemia major with blood transfusion dependency.

The study exclusion criteria were as those with delayed puberty, hypothyroidism or parathyroid gland dysfunction, renal failure, liver failure, growth hormone deficiency or person who using vitamin D or calcium-D.

Serum ferritin was measured by ELISA method. Osteoporosis diagnosis was performed using Dual Energy X-ray Absorptiometry (DEXA), which bone density of the spine vertebrates and femoral neck region were measured.

Evaluation of BMD in studied patients was performed by a radiologist with Lexxus device, made by APELEX Company, France. The mineral density was reported in g/Cm2. The comparisons with maximum values in similar age and gender group (T-Score) or with the average size of individuals of the same age and gender (Z-Score) were conducted to diagnose osteoporosis. The patients with serum ferritin levels higher than 1500 ng/dl were considered as cases, and patients with serum ferritin levels lower than 1500 ng/dl were considered as controls.

Experiments related to the functionality of other glands, liver, kidneys and electrolytes were simultaneous performed. Data were analyzed using SPSS 20, T-Test, Paired T-Test, x2 and Pearson and Spearman coefficients and, and $p<0.05$ was considered significant.

Results:

In overall, 70 patients were evaluated (24 (34.3%) males and 46 (65.7%) females). The mean age of studied patients was 27.6±4.97 years (15-36 years). The background characteristics of patients were shown in table 1. The mean age of the case group (ferritin levels higher than 1500) and the control group (ferritin levels less than 1500) was 28.66±4.59 and 26.54±5.16 years old, respectively (15-36 years).

The mean BMD of all patients in the femur and in the lumbar spine were 0.79±0.13 g/Cm_2 and 0.75±0.14 g/Cm_2, respectively. The prevalence of osteoporosis in the lumbar spine and femur of the studied patients were 48.6% and 20%, respectively. Osteopenia was also observed in the lumbar spine of 24 (34.3%) patients and in the femur of 33 (47.1%) patients. Similarly, the mean serum ferritin level of studied patients was 2234.91±1213.58 ng/dL. The BMD findings of femur in studied patients were normal [23 (32.9%)], Osteopenia [33 (47.1%)] and osteoporosis [14 (20%)]. And the BMD findings of lumbar were normal [12 (17.1%)], Osteopenia [24 (34.3%)] and osteoporosis [34 (48.6%)].

The mean serum ferritin level of patients was 2234.91±1213.58 ng/dl. The mean serum ferritin level in patients with femoral osteoporosis was 2865.31±882.7 ng/dL, while the mean serum ferritin

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levels in patients with osteopenia and normal density in the femur were 2324.56±1361.28 ng/dl and 1646.05±932.07 ng/dL, respectively (P = 0.001).

Also, the mean serum ferritin level in patients with osteoporotic lumbar vertebrae was 2532.69±1024.42 ng/dl, while the mean serum ferritin levels in patients with osteopenia and normal density in the lumbar spine were 2302.87±1500.05 ng/dL and 1236.17±338.16 ng/dL (P = 0.002), respectively.

The serum levels of calcium, phosphorus, PTH, TSH and T4 in all patients were normal. None of patients had the history of bone fractures.

In addition, femur and spine bone densitometry findings are indicated in tables 2 and 3 based on age, gender, number of blood transfusions per year, chelators used and the proper use of medication by the patient. In addition, the correlation between serum ferritin and bone densitometry of patients is mentioned in figure 1.

Table 1. Bone densitometry findings in patients with thalassemia major: Case&Control Groups. (n=70)

Densitometry findings	Control group (Ferritin≤1500)		Case group (Ferritin≥1500)	
	Femur	L.Vertebrae	Femur	L.Vertebrae
Normal	19(54.2%)	12(34.3%)	4(11.4%)	0(0%)
Osteopenia	15(42.9%)	13(37.1%)	18(51.4%)	11(31.4%)
Osteoporosis	1(2.9%)	10(28.6%)	13(37.2%)	24(68.6%)
Total	35(100%)	35(100%)	35(100%)	35(100%)

Table 2. Characteristics of patients according to the findings of the Femur densitometry

Patient Characteristics		Normal N (%)	Osteopenia N (%)	Osteoporosis N (%)	P-value
Age Group	<26 year old	8 (36.4)	8 (25)	5 (31.5)	0.665
	≥26 year old	14 (63.6)	24 (75)	11 (68.7)	
Sex	Male	6 (26.1)	14 (42.4)	4 (28.6)	0.395
	Female	17 (73.9)	19 (57.6)	19 (71.4)	
Times of blood transfusion annually	12-15 times	15 (68.2)	16 (50)	7 (43.7)	0.264
	15-18 times	7 (31.8)	16 (50)	9 (56.3)	
Chelators used	Osveral+Despheral	14 (63.6)	15 (46.9)	10 (62.5)	0.392
	Osveral+Despheral+Deferiprone	8 (36.4)	17 (53.1)	6 (37.5)	
Method of Use	Regular	19(86.4)	20 (62.5)	9 (56.3)	0.086
	Irregular	3 (13.6)	12 (37.5)	7 (43.7)	
Total		22 (100)	32 (100)	15 (100)	-

Table 3. Characteristics of patients according to the findings of the lumbar vertebral bone densitometry

Patient Characteristics		Normal N (%)	Osteopenia N (%)	Osteoporosis N (%)	P-value
Age Group	<26 year old	5 (41.7)	7 (30.4)	9 (25.7)	0.581
	≥26 year old	7 (58.3)	16 (69.6)	26 (74.3)	
Sex	Male	4 (33.3)	9 (37.5)	11 (32.4)	0.918
	Female	8 (66.7)	15(62.5)	23 (67.6)	
Times of blood transfusion annually	12-15 times	10 (83.3)	13 (56.5)	15 (42.9)	0.051
	15-18 times	2 (16.7)	10 (43.5)	20 (57.1)	
Chelators used	Osveral+Despheral	5 (41.7)	14 (60.9)	20 (57.1)	0.539
	Osveral+Despheral+Deferiprone	7 (58.3)	9 (39.1)	15 (42.9)	
Method of Use	Regular	10 (83.3)	18 (78.3)	20 (57.1)	0.114
	Irregular	2 (16.7)	5 (21.7)	15 (42.9)	
Total		12 (100)	23 (100)	35 (100)	-

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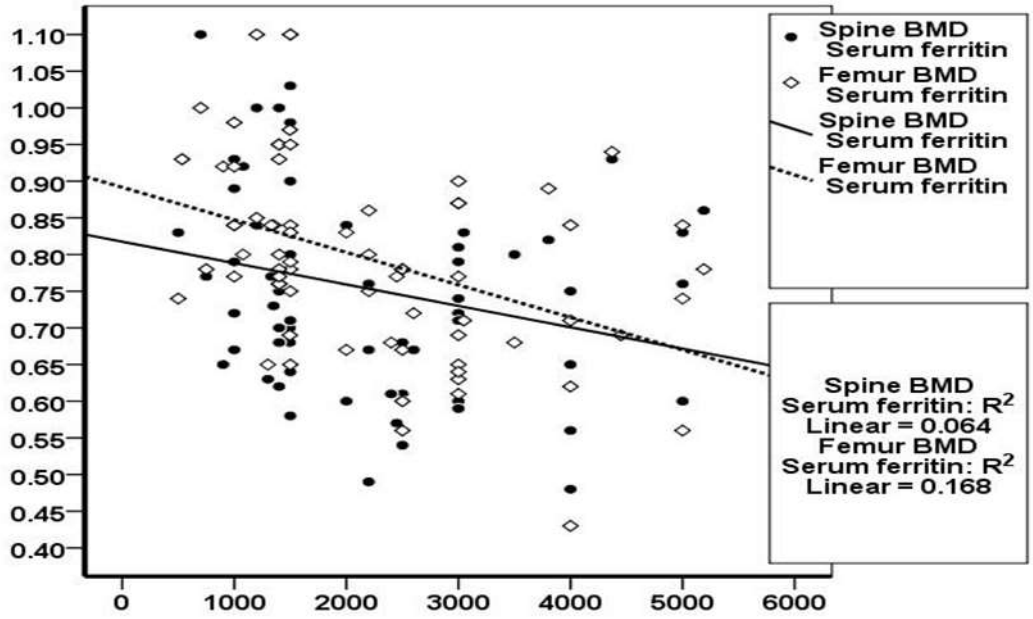

Fig 1.Correlation between serum ferritin level and densitometry findings in the study groups (n= 70)

Discussion:

Our study showed a significant and indirect relationship between serum ferritin levels and bone density of femoral and lumbar region. Iron deposion may be a cause of bone damage. And our study suggests that the serum ferritin levels in studied patients can be an appropriate indicator of bone density estimation, and maybe prediction of fractures.

Mean serum ferritin levels in patients with osteoporosis of the lumbar spine were 2532.69±1024.42 ng/dL, while the mean serum ferritin levels in patients with osteoporosis and normal BMD of the lumbar spine were 2302.87±1500.05 ng/dL and 1236.17±338.16 ng/dL (P=0.002), respectively (figure 1).

Karimi et al.s showed no significant association between BMD and Bone Mineral Content (BMC) with biochemical and hematological parameters, but both parameters correlated significantly with hemoglobin level. In clinical-pathological evaluations, the serum levels of calcium, phosphorus, alkaline phosphatase, hemoglobin and ferritin were measured. In their study, the mean age of patients was 13-14 years old, [11] while in the current study; the mean age was about 27. Similarly, the average spine BMD in patients with thalassemia major was significantly lower than the control group (0.60±0.08 and 0.76±0.05 g/Cm2, respectively).

However, there were no significant differences on BMD between beta thalassemia and thalassemia intermedia groups. The mean BMD in patients with thalassemia major having hemoglobin levels greater than 10 mg/dL was significantly lower, but other biochemical and hematological parameters as well as blood transfusion events, gender and therapeutic chelators showed no impact on BMD similar to our study[11].

Although in other study a correlation between the height, age and BMD were found [12]. Also, in Shamshirsaz et al.'s study, the bone density disorders of lumbar spine were correlated with chelating therapy duration. This difference could be due to a greater number of studied patients in the study. In this study conducted on 220 patients with thalassemia major, zinc blood levels showed a significant relationship with lumbar spine bone density [13].

In another study in Turkey that was done on 25 patients with thalassemia major with an average age of 18 years in 2004, the bone density of the lumbar spine and proximal femur were measured using Dual X-ray Absorptiometry method. In this study, the bone density of the lumbar vertebral column (0.633±0.168) and femoral bones (0.695±0.119) in the patient group showed significant differences compared to the controls (0.851±0.146 and 0.785±0.130, respectively). [14]

Examining bone related disorders in 18 patients with thalassemia showed a significant correlation between serum ferritin levels and the bone density between control (1.15±0.25) and patient (0.86±0.03) groups. In this study, the amounts of potassium, phosphate and serum ferritin in the patients group were 4.5±0.05 mEq/liter, 3.72±0.09 mg/dl and 1366.6±253.9 ng/ml, respectively. The same values for the control group were 3.6-5, 2.79-4.342 and 50-100, respectively [4].

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Unlike previous studies, in a study on children with beta -thalassemia, no significant relationship was found between BMD and serum ferritin levels. This can be due to small sample size, measurement errors or chelating therapy type. Another possible reason to explaining the lack of significant correlation between serum ferritin levels and bone density is the possible serum ferritin tolerance. In these experiments, serum ferritin levels were measured at a given moment, and its changes at different times were not determined. However, a significant shorter height, lower sexual maturity, and lower density values were seen in the patient group [15].

These results confirmed another study by Jensen et al. on 82 thalassemia patients (44 women with the mean age of 27 years, 38 males with the mean age of 25 years). In this study, the mean serum ferritin level at the time of study was 2733 mg/l, showing no significant association in patient group compared with control group (with a standard deviation of 5798 mg/l for serum ferritin levels), although there was a significant relationship between gender (male) and the severity of low bone mass [9].

Arjmandi et al. during 2004-2006 performed a study on 273 patients with thalassemia major (137 males and 136 females) and 32 patients with thalassemia intermedia (13 males and 19 females). The mean age was 14±6.5 and 13.4±6.5 years, respectively. They examined the relationship between BMD and biochemical and hematological parameters. In this study, no significant difference was found between osteoporosis patients and the control group regarding Height Standard Deviation Score (HSDS). This study showed correlation of bone density with serum ferritin levels in the radius region. Similarly, no significant correlation was found between bone density and serum levels of calcium, zinc, phosphorus, and magnesium [16].

Patients with thalassemia are prone to various conditions including bone disorders. Health maintenance of bone tissue in such patients is subject to assessment of the bones health with a technique, which should be highly accurate and reliable, easy to use and inexpensive.

In conclusion, the current study was showed significant differences between the mean serum ferritin levels in patients with thalassemia major and different bone mineral densities (normal, osteopenia, and osteoporosis). Thus, the patients with thalassemia major with lower bone density had significant higher serum ferritin levels compared to the patients with normal bone density. We recommended to more study of correlation between serum ferritin levels and bone density in people with thalassemia to assess bone health by this mentioned serum index.

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Conflict of interest: The authors declare that they have no conflict of interest.

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