

LUMBOSACRAL BONE DENSITOMETRY IN CHILDREN WITH B-THLASSEMIA MAJOR

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Abstract

Background: Skeletal changes and bone complications in patients with beta thalassemia major are common and risky. We aim in this study to early detection of low bone density in children with thalassemia major thus overcome any asymptomatic skeletal changes and pathological fractures.

The methods : this study is a cross sectional conducted in the center of hereditary blood disorders in alzahra teaching hospital for the period between 1st of October 2011 to end of November 2012. Fifty, randomly selected (selecting one patients every five of them) beta thalassemia major patients from a total of (685 patients) registered in the centre were evaluated for bone marrow densitometry (BMD). Patients were classified according to their ages in 3 main groups , group A (2 – 5 yr) , group B (6 – 10 yr) and group C (11 – 15 yr) . Dual energy x-ray absorptiometry (DEXA) was performed in lumbar regions of those patients . The Z-scores were measured from bone density values according to age and gender. The Z score less than -2.5 was taken as cut off value for osteoporosis, and between -1 and -2.5 as osteopenia. Biochemical and hormonal parameters were recorded and analyzed .

Results : The patient age mean was (15 ± 5.5 years) and BMD mean of spine was (-2.6500 ± 0.9). Mean Hb. Was (9.01g/dl) . All groups of patients with high serum Ferritin level , and (10 %) with hypocalcemia , (26%) had hypophosphatemia , (38 %) with high alkaline phosphates enzyme level. BMD was low in all patients of groups C (100%) , (77.78 %) of group B and (52.63 %) of group A ($p = 0.048$) , there is a significant relation between high levels of serum ferritin and BMD ($p = 0.0046$) While there is no significant relation between S.Ca , S.Ph. , S.ALP level and BMD .

Conclusion: present study show that patient of beta thalassemia major may show evidence of low BMD even in younger age group , and those with no clear clinical presentation of bone disease .

Key message: Regular assessment of BMD, to detect any skeletal changes before development of osteoporosis and thus overcoming pathological fractures .

Introduction Thalassemias are genetic disorders in globin chain production.

Thalassemia syndromes are the most common genetic disorder on world-wide bases which is inherited as an autosomal recessive bases^[1] .

Thalassemia syndromes either include defect in production of alpha α globin chain where α thalassemia are usually caused deletion of one or more globin gene or the defect is in the β chain production. In β thalassemia the condition may also be due to gene deletion but more commonly is the consequence of abnormalities in the reading or processing of DNA.^[2]

Bone complications the bone pathological changes can be seen only in poorly controlled thalassemic patients because regular blood transfusion and well controlled

hemoglobin levels may prevent these bony deformities. These deformities will be apparent after one year in the form of trabecular changes and cystic formation in small bone and thickening of the cortex and increase of medullary space of long. Skull x-rays will show the characteristic picture of "hair-on-end" appearances. [3].

Thalassemia facies occur because of overgrowth of maxilla and absence of cavitation of nasal sinuses that lead to prominence of upper incisors and separation of orbits. [3, 4]

Osteoporosis Osteopenia Syndrome (OOS)

Osteoporosis is a disease of skeletal system that is characterized by low bone density and microarchitectural changes that lead to increase bone fragility and easy fracture. [5] With improvement in life expectancy of thalassemic patient, osteopenia osteoporosis syndrome (OOS) is an important cause of bone pain and fractures in those patients. [6]

Many researches prove a decrease in bone mass in thalassemic patients (Chatterjee, 2000; Morabito, 2004; Pignatti, 2006b; Chan, 2002; Voskaridou, 2003). [7] The causes of OOS in thalassemia syndromes are multifactorial such as bone marrow expansion as a result of ineffective erythropoiesis, anemia, haemosiderosis, delayed puberty, use of chelating agents, multiple endocrinopathies, low level of vitamin D and genetic factors. [8]

Diagnosis and investigations

Those patients are commonly presented by pain in the bone and it may be associated with past history of fractures. About 20% of patients have no clinically apparent signs and symptoms. [9]

(A) DEXA scan

It is the best way to assess the bone mineral density (BMD).

(Fig.1) **WHO criteria for diagnosis of OOS.** ^[10]

Osteoporosis

BMD > 2.5 SD below the young normal mean (T-score) or standard deviation in relation to patient's age (Z-score) .

Osteopenia

BMD > 1.5 – 2.5 SD below the young normal mean (T – score) .

Biochemical

All patients should be assessed in the following biochemical study: 25 (OH) vitamin D₃ , paraathyroidhormones, calcium , phosphate , liver function tests, (alkaline phosphatase , ALT , billirubin , albumin) , FSH , LH , testosterone and estradiol assays

(C) Radiology

Antero-posterior and lateral X-ray of the spine to exclude fractures.

(D) MRI

Magnetic resonance imagaing (MRI) of the spine should be done to assess the extramedullary erythropoiesis , and also to check for other bone deformities.

(E)evaluation of iron load and chelating agent.

Management ^[9]

The goal of managements is to increase BMD score and decrease the risk of fracture.

Therapeutic options

A lot of treatment modality are present for treating thalassemic patent with osteopenia-osteoporosis .The choice of treatment was determined by the patient age, the thalassemia type such as frequency of blood transfusion , severity of sign and

symptom, previous fractures, treatment taken , other of risk factors of nephrocalcinosis and associated hypogonadism, hyperparathyroidism. [9]

Fig.2 : Therapeutic options for OOS. [10]

Diet and exercise .
Vit.D and calcium supplementation .
Sex hormones replacements in HRT.
Anti-resorption agents –Bisphosphonate .
Combination therapy - Bisphosphonate + HRT.

Monitoring of treatment

The management should be followed by biochemical parameters and DEXA scan should be done to the spine and neck of femoral to calculate the T-scores. An increase of 1 – 2 % each year is suggested in the neck of femur. After 3 years of pamidronate , usually the BMD effect remain the same. Also long –time treatment for more than 5 years is not recommended as it may cause osteosclerosis.

Management of hypogonadism must be monitored from assessment of serum sex steroid levels. Vitamin D therapy may carry the risk of nephrocalcinosis and bisphosphonate so it should be given with caution. Thalassemic patients who is on thyroxine and steroid treatment should be monitored because excess replacement can augment osteoporosis . [40]

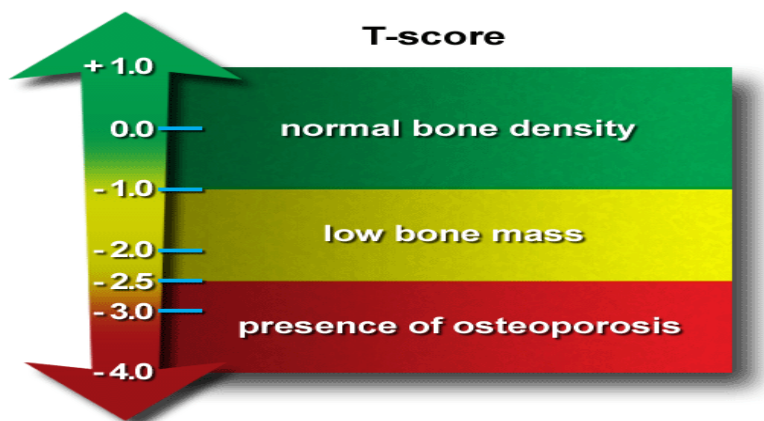
Bone densitometry is used to prove osteoporosis and to determine the risk of future fracture. It measures the bone density the hip, vertebra, forearm, and femur.

Bone densitometry may be conducted by using x-rays, dual-energy x-ray absorptiometry (DEXA or DXA) or by quantitative CT scanning using special

software. Ordinary x-rays may show weak bones. However, at the time where bone weakness is clear on x-rays, the treatment is too late to be successful. Bone densitometry testing can detect reduced bone density at an earlier stage so the treatment may be helpful. [11]

First, BMD result is compared with the BMD results from a young healthy (25-35 years old) of similar gender and race. The standard deviation (SD) is the difference between BMD and that of the young healthy adults. This result is called T-score. When the T-scores are positive it means that the bone is healthy and strong; when the T-score is negative it means that the bone is weak.

The WHO defines osteoporosis according to the following figure [12]:



- A T-score within 1 SD (+1 or -1) of the young adult mean indicates normal bone density.
- A T-score of 1 to 2.5 SD below the young adult mean (-1 to -2.5 SD) indicates low bone mass.
- A T-score of ≥ 2.5 SD below the young adult mean (> -2.5 SD) indicates the presence of osteoporosis.

THE METHODS: A total number of fifty (50) beta thalassemia major , regularly transfused patients at Al-zahraa' teaching hospital in thalassemia centre containing (685 registered patients) were randomly selected from visitors of that centre selecting one patients every five of them in a cross sectional study from 1st. of October 2011 to 30th of November 2012 . With ages between (2 – 15) years age. Permission had been taken from patients for legal and ethical purposes . Bone mineral densit (BMD) of lumbar region (L2 – L 4) using deual X-ray absorbiometry scan (DEXA scan) , (Dexxum3 osteosys) was done by a radiologist at Al-Sader teaching hospital / Alnajaf city .Patient sent in a regular schedule , as two patients / week separately in a total period of (12 months) .Results collected and interpreted depending on WHO diagnosis criteria of BMD when T-score < (- 2.5) considered as osteoporosis and between (-1 to - 2.5) as osteopenia. Blood collected , analyzed for : S.Ca. , S.Ph. , S.ALP , PTH , S.ferritin for each patient. Data interpreted using SPSS version 18 .Results considered stastically significant with (p value < 0.05) .

THE RESULTS: fifty (50) patients , 37 (74 %) were males and 13 (26 %) were females ,age ranged(2 years - 15 years), patients divided into mainly 3 age groups as shown in (fig. :4).

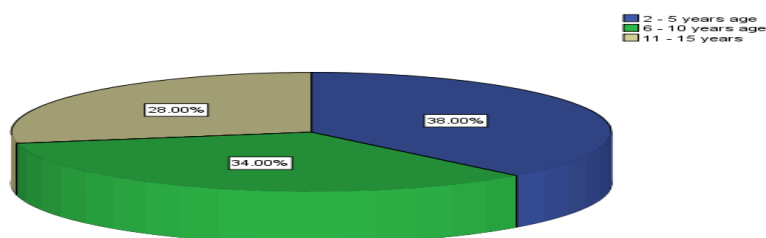


Fig 4:Age distribution of patients included in the study.

Table . 1 : Mean , SD and percentages of patients with abnormal DEXA scan

NO.		Mean	SD	Osteopenia <i>n</i> = 6	Osteoporosis <i>n</i> = 31
Z-score	50	-2.6500	8.23407	12 %	62 %
T – score	50	-3.9596	6.46615	12 %	62 %

Table 2 : Mean , SD , and ranges of all parameters studied

Parameters	Reference ranges	Mean	Std. Deviation
PTH level (pg./ml.)	9 – 65	33.6200	19.11820
Serum Ferritin (ng/mL)	30–300	3767.1000	4488.68780
Serum calcium (mg./dl)	8- 11	8.6800	1.19915
Serum phosphorus (mg./dl.)	3 – 4.5	3.7300	1.03238
Serum ALP (U./ml.)	60 -120	407.3000	158.73637

Table 3 : the relation of patient age with DEXA .

Age (years)	Normal DEXA scan	Abnormal DEXA scan	<i>p</i> value
2 – 5 (n=19)	9 (47.36%)	10 (52.6 %)	0.048
6 – 10 (n=18)	4 (22.22%)	14 (77.7%)	0.045
11 – 15 (n=13)	0 (0 %)	14 (100%)	

Hemoglobin level for all patients was above (8 mg./dl.) (mean = 9.0187) , related to readings of DEXA scan for normal and abnormal readings , there was no significant difference between two groups (*p* value = 0.4) . ; s.ca , s.ph. and s.ALP show no significant effect of them on DEXA scan readings in their normal or abnormal values . Parathyroid hormone levels ranges (60.4 +/- 19.9 to 61.3+/-30.2) in normal and abnormal DEXA readings respectively also show no significance.All 50 patients in all groups showed high levels of their s.ferritin (mean = 3767.1000) with significant changes in DEXA readings (Z-score > - 2.5 or more) with those of elevated s.ferritin (>1000 ng./ml.)

Table.4: Biochemical parameters and their relations with DEXA scan .

Parameter	Mean	Normal DEXA	Abnormal DEXA	P value
Hb. level	9.0187	8.2 +/- 0.9	8 +/- 1.1	0.4
S.calcium	8- 11mg./dl	8 +/- 0.9	8.8 +/- 1.2	0.644
S.phosphorus	3 – 4.5 mg./dl.	5.7 +/- 0.97	5.31 +/-1.25	0.887
S.AIP	60 -120U./ml.	307.7+/44.4	344.5+/1.33	0.229
PTH	9 – 65 pg./ml.	60.4 +/- 19.9	61.3+/-30.2	0.892
S.ferritin	30–300 ng/mL	-2.2+/- 0.33	-6.6+/-2.3	0.00466

Discussion: the incidence of osteoporosis in thalassemic patients have an average of 90% (range 52–96%) ^[13] , and the fractures incidence was 70% ^[14] .

The pathogenesis of osteoporosis could be a consequence of anemia on bone metabolism, or secondary to hemosiderosis of various endocrine glands, hepatic dysfunction, chronic illness and chelation therapy.^[15]

Karimi et al. ^[16] , studied BMD by DEXA in Iranian patients with beta thalassemia major and intermediate and found significant correlation between low bone mass and low Hb level. In current study , Hb.level show no any significant effect on BMD in all age groups included ($p = 0.4$) that may be explained by including those patients with controlled Hb.level that were 9g./dl. and above .

Studies by Benigno et al. ^[17] , showed relationship between BMD Z- scores and chronological age but without significance. In currnt study, there was a statistical significance ($p=0.048$) between chronological age and BMD scores explained by that increasing in age making patient more susceptible to skeletal changes such as widening in trabecular bone and so decrease in BMD (table :3).

As all our patients had serum ferritin levels above 1500 ng/ml. , it is possible to hypothesize negative effect of iron overload on degree of bone mineralization , so there was statistical significance between level of serum ferritin in high levels and BMD in an inverse way . ^[18] No available studies present relating high serum ferritin and low BMD.

We noted a high incidence of hyperphosphatemia both in patient and control with abnormal DEXA and there was no statistical significance between phosphorus levels and Z scores ($p=0.887$).

The present study (38%) had hyperparathyroidism which could be explained probably by low vitaminD levels that show no significant effect on BMD ($p = 0.892$).

Conclusions .The presence of low BMD in patients with beta thalassemia major inspite of absence of clinical symptoms related such as bone pain. so they should receive correct and early detection and management to prevent excessive bone expansion and thus decrease in BMD

Recommendations Children with beta thalassemia major should have their annual DEXA scan as part of regular follow up of BMD , to detect any skeletal changes and so earlier and prompt management before development of osteoporosis overcoming pathological fractures .

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