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ORGINAL ARTICLE

EVALUATION OF OSTEOPATHY AND VITAMIN D STATUS IN PATIENTS WITH BETA-THALASSEMIA MAJOR

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ABSTRACT

Background: The survival of patients with thalassemia major has progressively improved with advances in therapy; however, osteoporosis and cardiac dysfunction remain frequent complications. Adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk this study aimed to evaluate the density of bone mineral (BMD) and vitamin D status in patients with β-thalassemia major (β-TM). **Methods:** The current study was carried on thirty three β-thalassemic childrens who attend the Pediatric Hematology Clinic at Zagazig University Hospitals during the period from April 2018 to October 2018 (21 male and 12 female). Dual-energy X-ray absorptiometry scan was used to evaluate bone density and interpreted as Z-score which compared to the BMD of age, sex and ethnicity-matched reference population. Biochemical parameters such as calcium, serum ferritin (SF) and 25-OH Vitamin D have been evaluated. **Results:** there were significant increase in serum ferritine level, AST, ALT, ALP, total bilirubin and urea and decrease in total protien , serum albumin and criatinine in the thalassaemic patients than controls**.** There was significant low level of vitamin k2 in the thalassaemic patients than controls **Conclusion:** Osteopathy has a high prevalence in patients with β-TM and should receive an optimal transfusion and chelation therapy to prevent bone expansion. Calcium and Vitamin D should be routinely determined to prevent deficiency.

Keywords: Beta-thalassemia major, Osteoporosis, Osteopenia, 25 (OH) cholecalciferol.

INTRODUCTION

Beta-thalassemia syndrome is a blood disorders that are mainly caused by the reduced or absent synthesis of the beta chains of hemoglobin, that results in reduction of red blood cells (RBCs) hemoglobin, decreasing the RBCs production causing anemia [1,2]. Beta-thalassemia usually inherited as an autosomal recessive disease, more than 200 β-thalassemia mutations have been identified, in some of which severe anemia is produced [3]

Osteopenia and osteoporosis are common bone disease in thalassemia patients [4,5]. Osteoporosis mostly related with many risk factors, such as, disease duration, level of haemoglobin, iron toxicity, the puberty onset, nutritional deficiency and hormonal disorder [6,7].

Vitamin D is necessary for calcium homeostasis and skeleton mineralization. Vitamin D hydroxylated to 25-hydroxy vitamin D3 in the liver and regulated by parathyroid hormone, the excess of hydroxylation to 1,25-dihydroxyvitamin D3 passes to the kidney. Patients affected by thalassemia major progressively develop iron overload, and decrease of liver hydroxylation of vitamin D. Thus, low vitamin D levels is found in most cases.[(8)]

This study aimed to evaluate the density of bone mineral (BMD) and vitamin D status in patients with β-thalassemia major (β-TM).

METHODS

The current study was carried on thirty three β-thalassemic children who attend the Pediatric Hematology Clinic at Zagazig University Hospitals during the period from

April 2018 to October 2018, The sample size were chosen according to the diagnosis of beta thalassemia major based on standard criteria [9], (21 male and 12 female) with a mean age 15.78±3.9 years(range:10-20) . In addition, thirty three healthy children were selected as a control group age and sex matched (19 male and 14 female) with a mean age 14.78±2.9 years (range:11-19). Consents were obtained from the patients or their legal guardians before enrollment in the study. The work has been carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studied involving humans.

Inclusion criteria: Children with the diagnosis of beta thalassemia major, based on conventional clinical and hematologic criteria, Both sexe and Patients older than 10 years of age. **Exclusion criteria:** Children with known bone and metabolic diseas, Children with hepatic and renal impairments, Children less than 10 years old and Children with other chronic hematological anemia.

Written informed consent was obtained from all participants' parents and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans

All patients were subjected to full history taking (age, sex, height, weight, body mass index (BMI). Also, disease duration, blood transfusion, chelation, and previous treatments were recorded. The biochemical evaluation included determination of phosphorus, serum calcium, and 25-hydroxy vitamin D levels which estimated by chemiluminescence assay [10] (Deficient < 20 Pg/ul- Insufficient (20 to 30) Pg/ul- Sufficient (30 to 100) Pg/ul- Toxic > 100 Pg/ul).

All the patients underwent DEXA scan and density of bone mineral (BMD) were obtained at lumbar spine and total hip femoral neck. the "Z score" was calculated at these two sites following DEXA scan, Z score is the best parameter in children which calculated the number of standard deviations above or below the mean for the patient's sex, age and ethnicity. A Z score considered normal for −1.0 or higher value, score between −1.0 and −2.5 considered Osteopenia and score of −2.5 or lower considered osteoporosis [11].

Bone Mineral Density (BMD) was measured by the Dual Energy X-ray Absorption (DEXA) scan method.

Dignostic Gatiogry	**Z-score**
Normal	>-1
Osteopenia	-1 to -2.5
Osteoporosis	<-2.5

Statistical analysis

Data were collected, tabulated and analyzed by SPSS 20, software for Windows. According to the type of data qualitative represent as number and percentage , quantitative continues group represent by mean ± SD , the following tests were used to test differences for significance;. difference and association of qualitative variable by Chi square test (X^2) . Differences between quantitative independent groups by t test or Mann Whitney, correlation by Pearson's correlation or Spearman's . P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

The mean height (157.7±18.31cm), weight (52.24±11.3kg), and BMI (16.72±2.41kg/m^2) of patients were lower comparing to controls and there was a statistical significant difference as regard weight and BMI between the studied groups with lower level to the thalassemia patients compared with controls **(Table 1)**.

There was a significant lower mean serum calcium level in patients compared to the control group. There was a statistical significant difference in mean of serum phosphorus levels between the studied groups with high level in patients than controls. There was a statistical significant difference regarding the mean value of serum alkaline phosphatase between the studied groups. There was no statistical significant difference regarding the mean value of vitamin D between the studied groups, there was a statistical significant difference between the studied groups as regarding serum calcium, magnesium and phosphorus levels, and also there was significant difference between the

studied groups as regarding serum ferritin **(Table 2)**.

The mean BMD in thalassemia patients at lumbar spine was lower significantly compared to control group. also BMD at LT femur total hip was significantly lower compared to control group. There was a statistical significant difference between the studied groups according to DEXA scan **(Table 3)**.

There was a positive correlation between Calcium level and BMD at the two sites; it was (r= 0.116, P= 0.526) at lumbar spine and (r = 0.392, P = 0.026) at LT femur total hip. However, there was a statistical significant difference at LT femur total hip. Also, there was a positive correlation between the level of vitamin D and BMD at all the three sites with no statistical significant difference. Regarding the density of Bone mineral at all sites a negative correlation with age but with no statistical significant difference. No significant correlation for BMI but for serum ferritin there was negatively correlation with BMD in two sites **(Table 4)**.

Table (1): Comparison between the studied groups regarding anthropometric measurements.

Anthropometric measures	Thalassemia group	Control group	T	P
Height (cm): **Mean ± SD** **Range**	157.7±18.31 (133-189)	163.42±15.87 (144-188)	-1.358	0.179
Weight (kg): **Mean ± SD** **Range**	52.24±11.3 (35-73)	60.7±16.49 (40-86)	-2.43	0.018*
BMI (kg/m^2): **Mean ± SD** **Range**	16.72±2.41 (13.4-24.1)	22.08±2.1 (18.7-25.1)	-9.638	<0.001**

T= independent sample t test, *p<0.05 is statistically significant
****p ≤0.001 is statistically highly significant BMI: Body mass index**

Table (2) : Comparison between the studied groups regarding laboratory investigation:

Laboratory Investigation	Thalassemia group	Control group	T	p
Calcium (mg/dl): **Mean ± SD** **Range**	8.56±0.68 (7.2-9.8)	9.77 ± 0.5 (9.1-10.7)	-8.225	<0.001**
Magnesium (mg/dl): **Mean ± SD** **Range**	1.66 ± 0.23 (1.2-2.1)	2.27 ± 0.1 (2.1-2.4)	-13.571	<0.001**
Phosphorus (mg/dl) **Mean ± SD** **Range**	5.81 ± 0.96 (4.2-7.6)	5.11 ± 0.3 (4.5-5.5)	3.981	<0.001**
Alkaline phosphatase(IU/L) **Mean ± SD** **Range**	395.52±121.29 (122-675)	159.45±24.28 (113-201)	Z (-6.62)	<0.001**
Serum ferritin(ng/dl) **Mean±SD** **Range**	2231.15±1020.2 (869-3999)	83±32 (30-127)	4.8	<0.001**
Vitamin D (pg/dl): **Mean ± SD** **Range**	16.32±3.41 (11- 25)	16.33 ± 5.71 (12.2-34)	t (-0.005)	0.996

****p≤0.001 is statistically highly significant**

Table (3): Comparison between the studied groups regarding results of DEXA scan for Thalassemia patients and controls.

Results of DEXA scan	Thalassemia group	Control group	Z`	P
BMD of lumbar spine: Mean ± SD Range	**0.62±0.11** (0.4-1.01)	**0.79±0.15** (0.5-0.97)	**t (-4.983)**	**<0.001****
Z score of L spine: Mean ± SD Range	**-1.98±1.15** (-3.7-1.4)	**0.49±1.01** (-0.9-1.9)	**-7.315**	**<0.001****
BMD of LT femur total hip: Mean ± SD Range	**0.73±0.11** (0.51-1.1)	**0.88±0.1** (0.7-0.98)	**t (-5.684)**	**<0.001****
Z score of LT femur: Mean ± SD Range	**-1.79**±1.11 (-3.28-1.8)	**0.89±1.13** (-0.8-2.1)	**-9.246**	**<0.001****

****p≤0.001 is statistically highly significant.**
Z` mann whitney test t independent sample t test

Table 4: Correlation of bone mineral density at lumbar spine (LS), , and left femur total hip in cases.

		BMD-LS	BMD-LT femur Total hip
Age	r P value	−0.052 0.776	−0.066 0.718
BMI	r P value	0.393 0.026	0.039 0.832
S. ferritin	r P value	-0.372 0.036*	-0.509 0.003*
Ca	r P value	0.116 0.526	0.392 0.026
Vit D levels	r P value	0.169 0.175	0.051 0.682

DISCUSSION

Many studies reported that osteopenia or osteoporosis in approximately 40–50% of well treated thalassemia major patients and reported as major cause of morbidity in these patients [12, 13]. Changes of bone in thalassemia patients may be due to the increase of marrow erythropoiesis and extensive iron deposition which lead to expansion of bone marrow cavities and reduce the volume of trabecular bone, causing a decrease in bone tissue and osteoporosis [14, 15], the deficiency of minerals like vitamin D and zinc and vitamins, cause worse bone health. Presence of endocrinopathies such as hypothyroidism, hypoparathyroidism, hypogonadism and diabetes mellitus could be contributed to bone disease [16,17].

In current study About two-thirds of our patients had reduced BMD Osteoporosis was reported in (36.4%) as well as osteopenia (30.3%) from total number of thalassemic patients and these finding matching with study by **Shawkat et al.** [(18)].

In the present study, all anthropometric measures were significantly lower in Thalassemic patients than control group and these results compatible with a study done by **Meena et al.** [(19)] who found that all anthropometric measurements were low in thalassemia children compared with controls .These changes can be explained by chronic illness and endocrinal changes due to iron overload.

Calcium and magnesium concentration was significantly decreased in thalassemic

patients compared to controls. On the other hand, phosphorus was significantly increase in thalassemic patients. These results are consistent with that reported by **Nawar et al. (20)**.

The current study demonstrated that there was a statistical significant difference between the studied groups according to DEXA scan which agree with the study of **Sahni et al. (21)** who found that there was positive association between vitamin C supplementation and one or more BMD sites.

In the current study, the body mass index and mean weight of patients were significantly lower than in control group. The mean height of patients was lower without statistical significant difference. These changes could be due to chronic illness, nutritional deficiency and endocrinal changes according to iron overload **(19)**.

Vitamin 25-OH-cholicalciferol deficiency was detected in most thalassemia patients in the current study, the mean value was 16.32±3.4. about 84.8% of the studied thalassemia patients had vitamin D deficiency and 15.2% was insufficient. Nutritional deficiency was the main cause of vitamin D deficiency in thalassemic patients. But there was no statistical significant difference in the levels of vitamin 25-OH-cholicalciferol between patients and control group. This may be due to the prevalence of vitamin D deficiency in the general population in Egypt and our patients taken vitamin D supplement but in insufficient dose and this result agreement with study of **Meena et al (19)**.

There was a negative correlation in density of bone mineral at all sites without statistical significance with age. This proposed that BMD decrease with advanced age, as reported by a study of Indian thalassemia children which their ages ranged from 10 to 25 years old [22]. Our study showed that there was a positive correlation between BMD and levels of vitamin D but without statistical significance. Also, there was a positive correlation between level of calcium and BMD at two sites but there statistical significant difference only at LT femur total hip. Thus, the present study proposed that low serum vitamin D levels and low serum calcium levels could be an important predictor of low bone mineral density in thalassemics.

In this study, the density of bone mineral at all sites were statistically significant negative correlation with serum ferritin and this was in agreement with a study by **Nesheli and Farahanian** (23) on Seventy children and adolescents with major thalassemia but disagreement with other studies who report no significant correlation between serum ferritin and BMD (15,16).

Conclusion : Osteopathy has a high prevalence in patients with β-TM and should receive an optimal transfusion and chelation therapy to prevent bone expansion. Calcium and Vitamin D should be routinely determined to prevent deficiency.

Limitation of the Study: the limit of this study was that DEXA not available and affordable.

No Conflict of Interest.
No Financial Disclosures.

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