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Bone metabolic disorders among patients with major β thalassemia: A cross-sectional study from Iran

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Abstract

Objectives: One of the chronic complications associated with β-thalassemia major is bone metabolic disorder. The present study was designed to assess the prevalence of bone metabolic disorders and associated risk factors among the patients.

Methodology: A cross-sectional study was conducted. The study population consisted of major β-thalassemia patients. Levels of several serum elements were measured. Bone mineral density (BMD) of lumbar spine and the neck of the femur were also assessed. All collected data were analyzed to determine the frequency of bone metabolic disorders and the related risk factors.

Results: Fifty-two patients with mean age of 22.46 ±3.36 years entered the study. The mean height of participants was 162.35±9.75 Cm and 21% of them were short stature. Regarding blood biochemical factors, ferritin in 14 (26.9%), 16 (30.8%), and 22 (42.3%) subjects were <1000, 1000-2000, and >2000 ng/ml, respectively. Hypophosphatemia was observed in 28.8% and 3.8% of participants had hypocalcemia. Vit D_3 insufficiency was frequently reported in the participants (57.7%). Concerning BMD values, more than 75% of participants showed degrees of bone mineral disorders. Analysis of data showed that sex was a significant factor affecting femur (p=0.003) and spine BMD status (p=0.039). No relationships were observed between BMD status and measured serum elements (p>0.05).

Conclusion: The findings of present study revealed that β-thalassemia patients were at great risk of bone metabolic disorders. Although the results showed no correlations between BMD levels and several blood biochemical factors, β-thalassemia major patients should be monitored for potential blood biochemical imbalance and their associated long-term consequences.

Keywords: β-thalassemia major; Bone mineral density; Lumbar Vertebra; Femur; Serum; Elements

1. Introduction

β-thalassemia is one of the most common genetic diseases worldwide. This hereditary disorder is characterised by a reduction in β-globin chain synthesis (1). The severe form of thalassemia occur in individuals who are homozygous or compound heterozygous, resulting in chronic hemolytic anemia (2, 3). Thalassemia major can be managed through blood transfusion; however, there are severe complications related to blood transfusion and iron overload. To reduce

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the risk of iron accumulation in the tissues, iron chelation therapy and splenectomy are implemented. Other medical interventions, such as bone marrow transplantation and gene therapy are also used to improve patient's survival (2).

One of the chronic complications associated with β-thalassemia major is bone metabolic disorder (4). Osteoporosis and osteopenia are prominent morbidities among β-thalassemia patients (5).

Evidence has shown that about 40%-70% of thalassemia patients suffer from bone metabolic disorders, which can be detected by decline in bone mineral density (BMD) and bone turnover. Skeletal and growth abnormalities, including growth failure, delayed bone age, and spondylometaphyseal abnormalities, also occur in patients due to bone marrow expansion resulting from impaired erythropoiesis. Insufficient osteoblastic formation and augmented osteoclastic resorption in thalassemia patients may begin in childhood and worsen with age (4, 5, 6, 7, 8). Additionally, several factors indirectly contribute bone metabolic disorders in thalassemia major patients. Iron overload, endocrine complications, chronic liver disease, renal dysfunction, iron chelation therapy, and deficiencies in 25 (OH) vitamin D (Vit D_3) and zinc are some of them (7).

Annually, about 23,000 babies are born with homozygous β-thalassemia major in low- and middle-income countries. The frequency of thalassemia varies geographically, with the highest prevalence reported in African, Asian, and Mediterranean countries. Among these, Malaysia, Iran, and Greece have the greatest numbers of cases (1, 8, 9). Concerning the high prevalence of disease in our country, its severe complications, prolonged adverse outcomes, and significant burden on healthcare system, the present study was designed to assess the prevalence of bone metabolic disorders and their risk factors among patients with major β-thalassemia. The results of this study may suggest appropriate decisions to improve the quality of life for these patients.

2. Materials and Methods

A cross-sectional study was conducted at Imam Khomeini Hospital Complex in Tehran, Iran, in 2019. The study population consisted of major β-thalassemia patients aged 10-25 years who attended our academic center for blood transfusion. The exclusion criteria were age below 10 or above 25 years, pregnancy, and conditions affecting bone mass, such as long-term corticosteroid consumption. Before enrollment, all participants provided written informed consent.

patients' demographic data, including age (years), sex, weight (Kg), height (Cm), and body mass index (BMI; kg/m^2) were extracted from their medical records and entered into a checklist. Short stature (height percentile <3%) was determined based on CDC chart and the height percentile adjusted for age and sex (2, 10, 11). Patients' BMI values were categorized into three groups: below18.4 as underweight, 18.5-24.9 as normal, and above 25 kg/m^2 as overweight (12).

To determine blood biochemical parameters, 5 ml of venous blood was drawn, labeled, centrifuged, stored at -70^0 C, and sent to the laboratory. Levels of serum total calcium (Ca; spectrophotometric method), phosphorus (P; atomic spectrophotometric method), alkaline phosphatase (ALP; spectrophotometric method), ferritin (radioimmunoassay), Vit D_3 (radioimmunoassay), and parathyroid hormone (PTH; immunochemiluminometric) were measured and recorded. Blood Vit D_3 concentrations <10, 10-30, >30 ng/ml were considered as deficient, insufficient, and sufficient, respectively. Moreover, blood total Ca<8 mg/dl, P<2.5 mg/dl, and PTH below the reference range (10-66 pg/ml) were classified as hypocalcemia, hypophosphatemia, and hypoparathyroidism, respectively (13, 14). The reference range for ALP was 40-150 U/L (15).

A bone mineral density test was performed using dual x-ray absorptiometry (DEXA) for all patients. Accordingly, bone mineral density (BMD) and content values of lumbar spine (L1-L4) and the neck of the femur were assessed. Based on calculated Z-scores, the patients were categorized into three groups: osteoporosis (Z-score<-2.5), osteopenia (-1<Z-score<-2.5), and normal (Z-score>-1) (16). Finally, all collected data were analyzed to determine the frequency of bone metabolic disorders among patients with β-thalassemia major which was the primary objective. The relationships between variables were also evaluated to identify any risk factors for bone metabolic disorder as the secondary outcome.

2.1. Sample size

The similar studies have shown the prevalence of metabolic disorders in about 50% of β-thalassemia patients. Using the following formula, the sample size of 52 patients was considered as sample size.

$N = \frac{Z1 - \frac{\alpha^2}{2}\ p.q}{d^2}$ d=0/136 $Z1 - \frac{\alpha^2}{2} = 1/96$ n = 52

2.2. Ethical Consideration

The present study was approved by the Ethical Committee of the Tehran University of Medical Sciences (ID:IR.TUMS.IKHC.1398.047) based on the Helsinki declaration. Written informed consent was given from the participants. All data were considered confidential and no extra cost was imposed to subjects regarding paraclinical examinations.

2.3. Statistical Analysis

Recorded data were analyzed using SPSS version 26. The categorical data were presented as number (percentage) and continuous data as mean±standard deviation. The Independent t-test, Chi-Square, and Mann-Whitney U tests were implemented where applicable. P value<0.05 was considered as statistical significance level.

3. Results

Fifty-two patients including 27 females (51.9%) and 25 males (48.1%) with mean age of 22.46±3.36 years (Min: 13; Max: 25 years) entered the study. The mean height of the study population was 162.35±9.75 Cm (Min: 130; Max: 180) and 21% of them were short stature (< percentile 3%). The mean of patients' BMI was 20.4±3.49 kg/m^2 (Min: 13.6; Max: 36.1). The most patients (69.2%) had normal BMI and the least (7.7%) were overweight.

Regarding blood biochemical factors (Table 1), ferritin in 14 (26.9%), 16 (30.8%), and 22 (42.3%) subjects were <1000, 1000-2000, and >2000 ng/ml, respectively. Hypophosphatemia was observed in 28.8% and 3.8% of participants had hypocalcemia. Thirty-five patients (68.6%) had normal serum ALP concentrations and the others showed abnormal ranges. Although Vit D_3 deficiency was not frequent among patients (1.9%), Vit D_3 insufficiency was frequently reported in the participants (57.7%). Forty-six patients (88.5%) had normal ranges of PTH levels and 3 (3.8%) had values below the reference range. Two patients also had normal PTH values with decreased Ca concentrations.

Concerning BMD values, the mean of spine BMD was -2.404±1.246 (Min=-4.60; Max= 0.7) and the mean of femur BMD was -1.545±0.960 (Min=-4.90; Max= 0.50). As values regarding femur and spine BMD are depicted in Table 1; more than 75% of participants showed degrees of bone mineral disorders. Based on spine BMD values, about half of included participants (48.1%) showed osteoporosis and with respect to femur BMD, more subjects demonstrated osteopenia (57.7%).

Analysis of data showed that sex was a significant factor affecting femur (p=0.003) and spine BMD status (p=0.039). Based on femur BMD values, osteopenia was more frequent among male than female subjects, while osteoporosis was more frequent among female patients. Conversely, the results showed osteopenia in females and osteoporosis in males were more frequent according to spine BMD values. Moreover, parameters related to height (p<0.001), weight (p=0.007), serum P (p=0.005), and Vit D_3 (p=0.048) were significantly different between female and male participants (Table 2). As data are depicted in Table 3, more analyses showed no relationships between BMD status and blood levels of ferritin, Ca, P, ALP, PTH, and Vit D_3 (p>0.05). No relationship was also found between BMD values and BMI status (p>0.05).

Table 1 Clinical characteristics of the included participants [a]

Variables	Mean	SD	Minimum	Maximum
Blood biochemical factors				
Ferritin (ng/ml)	2607.5	2618.6	231	14250
Calcium (mg/dl)	9.3	0.5	7.2	10.3
Phosphorus (mg/dl)	4.2	0.8	2.4	7.3
Alkaline phosphatase (Iu/L)	193.1	134.9	43	713
Vitamin D_3 (ng/ml)	29.7	13.8	9.0	64.9
Parathyroid hormone (pg/ml)	41.4	33.9	5	241
BMD (n%)				

Femur:				
Normal (z-score > -1)	13 (25.0)			
Osteopenia (z-score: -1 to -2.5)	30 (57.7)			
Osteoporosis (z-score < -2.5)	9 (17.3)			
Spine:				
Normal (z-score > -1)	9 (17.3)			
Osteopenia (z-score: -1 to -2.5)	18 (34.6)			
Osteoporosis (z-score < -2.5)	25 (48.1)			

a. The categorical data are presented as number (percentage) and continuous data as mean ± standard deviation

Table 2 Comparison of demographic and clinical characteristics in male and female participants[a]

Variable	**Groups**	**Females (n=27)**	**Males (n=25)**	**P-value**
Age; y		23.0 ± 3.3	21.8 ± 3.3	0.203[b]
Height; cm		156.7 ± 7.8	168.4 ± 7.9	< 0.001*[b]
Height percentile	< 3%	21 (77.8)	20 (80.0)	0.846[c]
	> 3%	6 (22.2)	5 (20.0)	
Weight; kg		50.5 ± 8.5	57.3 ± 9.2	0.007*[b]
BMI; kg/m^2		20.9 ± 4.2	20.1 ± 2.5	0.425[b]
BMD (femur)	Normal (z-score > -1)	4 (14.8)	9 (36.0)	0.003*[c]
	Osteopenia (z-score: -1 to -2.5)	14 (51.9)	16 (64.0)	
	Osteoporosis (z-score < -2.5)	9 (33.3)	0 (0.0)	
BMD (spine)	Normal (z-score > -1)	6 (22.2)	3 (12.0)	0.039*[c]
	Osteopenia (z-score: -1 to -2.5)	12 (44.4)	6 (24.0)	
	Osteoporosis (z-score < -2.5)	9 (33.3)	16 (64.0)	
Serum Calcium; mg/dL		9.4 ± 0.4	9.2 ± 0.6	0.097[b]
Serum Phosphor; mg/dL		3.9 ± 0.7	4.6 ± 0.9	0.005*[b]
Serum ALP; IU/L		176.4 ± 139.5	211.1 ± 130.3	0.360[b]
Serum PTH; pc/mL		42.2 ± 22.7	40.7 ± 43.4	0.876[b]
Serum Vitamin D_3; ng/mL		25.6 ± 11.1	32.8 ± 14.0	0.048*[b]
Serum Ferritin; mg/L		2598.1 ± 2405.0	2613.9 ± 2882.0	0.983[b]

Abbreviations: ALP = alkaline phosphatase, BMD = bone mineral density, BMI = body mass index, PTH: parathyroid hormone.; **a.** The categorial data are presented as number (percentage) and continuous data as mean ± standard deviation.; **b.** Independent t-test.; **c.** Mann-Whitney *U* test.; ***** Statistical significance level at p-value < 0.05.

Table 3 The correlations between blood biochemical parameters and bone mineral density

Variables	**P value**	
	BMD (femur)	BMD (spine)
BMI	0.753	0.148
Ferritin	0.584	0.113
Calcium	0.972	0.926
Phosphorus	0.997	0.325

Alkaline phosphatase	0.958	0.965
Vitamin D_3	0.457	0.103
Parathyroid hormone	0.367	0.830

4. Discussion

Thalassemia as a chronic inherited disease adversely affects endocrine and metabolic systems resulting in bone disease (17). Iran is a country with the highest population of β-thalassemia major patients (9). Although there has been great progress in knowledge regarding the etiology and manifestations of the disease (18), bone metabolism disorders in these patients with different demographic, hormonal, blood biochemistry, and nutritional status need more consideration. Hence, the present study aimed to demonstrate the prevalence of bone mineral disorders in 10 to 25-years old patients who referred to our clinic.

Considering femur BMD, the results of present study showed that 57.7% of participants had osteopenia and 17.3% had osteoporosis. According to the spine values, the results showed higher rate of osteoporosis by 48.1% compared to the osteopenia rate (34.6%). These findings revealed that β-thalassemia patients are at great risk of bone mineral disorders. Bone metabolic disorders in β-thalassemia patients are due to bone marrow hyper activities and decrease of trabecular bone mass (19). In accordance with our results, a study from Iran reported close prevalence rates regarding osteoporosis in lumbar spine (50.7%) and femur (10.8%) among 203 β-thalassemia major patients with mean age of 15.2±3.2 years (20). Another investigations from Iran showed the higher prevalences; Hamidpour et al. reported osteoporosis and osteopenia in 63.4% and 36.5% of included β-thalassemia major patients with the mean age of 35.6±7.7 years (9). Other studies from different countries reported various frequencies based on population's demographic characteristics. For instance, Thavonlun et al. (21) from Bangkok showed osteopenia in 55.4% and osteoporosis in 38.4% (based on BMD T-score) of transfusion-dependent thalassemia patients with mean age 35.1 years. The other study from Iraq (22), reported osteoporosis in 21.3 % of 150 β-thalassemia major cases with mean age of 19.5±7.5 years. The diversity in the prevalence rates may correlate to several involving factors like participant's age, BMI, sample size of study, levels of treatment, care, and preventive measures.

According to the results, sex was a significant factor affecting femur and spine BMD status. This difference between BMD status of male and female participants may associate with significant differences in their height, weight, serum P, and Vit D_3 ($P<0.05$). On the other hand, an investigation by Mohajeri-Tehrani et al. (23) assessed the relationship between sex and bone density disorders among 114 β-thalassemia major cases. Their results demonstrated that there was no significant association between sex and such disorders.

The results of present study showed that 21% of included participants had short stature. This complication in β-thalassemia major patients may relate to different reasons like growth retardation, malnutrition, Ca, P, and Vit D_3 metabolism disorders, iron-chelating toxicity, abnormal pubertal development, delayed sexual maturation, and endocrinopathies (impaired growth, insulin-like growth factor 1, thyroid, and parathyroid hormones) (24, 25). In accordance to our findings, other studies have shown the relationship between β-thalassemia major and short stature; however, the reported frequency rates related to this complication were different. An investigation from Iran showed a higher rate by 32% in β-thalassemia major patients with mean age of 20±7 years (11). A Systematic Review and Meta-Analysis showed short stature in 48.9% of β-thalassemia major patients from five continents (1). The other study reported a frequent short stature complication by 60.2% among 56 children (aged less than 18 years) with β-thalassemia major and receiving regular blood transfusion (24). These diversities in the results may relate to the number of sample size, demographic, hereditary, and familial characteristics.

Concerning ferritin status, the results of present study showed that 73.1% of our participants had ferritin level above 1000 showing Iron overload. Furthermore, the high frequency rates of hypophosphatemia (29.84%), hypocalcemia (3.9%), Vit D_3 insufficiency (57.7%), and liver dysfunction (31.4% with abnormal ALP ranges) indicate that the large number of our patients did not receive early, regular, or efficient treatment and follow-ups. Hence, it should be noticed that β-thalassemia major patients were at great risks of biochemical imbalance and need more considerations to prevent long term consequences. In accordance to our findings, Yang et al. (26) determined that of 29 thalassemia major patients aged 20 years, 42.9% of the female and 23% of the male subjects had abnormal BMD values. They also showed a highly prevalent Vit D_3 deficiency among the patients; all female participants and 81.8% of male subjects had Vit D_3 deficiency (serum Vit D_3 ≤24 ng/ml). Kothimira et al. (27) also demonstrated that of 50 β-thalassemia major patients with regular blood transfusion and chelation therapy, 90% had ferritin levels >1000. Another investigation from Saudi Arabia (28) revealed the significantly high levels of serum ferritin (due to Iron overload) and low levels of Vit D_3

(possibly due to defective synthesis of Vit D_3 or secondary to hypoparathyroidism) in 69 β-thalassemia major patients. Of all participants, 89.9% had ferritin levels above 1000 and only 12% had normal Vit D levels (>24 ng/ml).

The results of present study revealed no correlations between BMD and several blood biochemical factors such as ferritin, Ca, P, ALP, PTH, and Vitamin D_3. These findings may relate to the small sample size, definitions of normal and low BMD values, and other important involving factors that may mask the role of these elements. Our results were confirmed by other investigations; Yang et al. (26) showed no correlations between BMD and corrected Ca, P, Vit D3, and ferritin levels. Kothimira et al. (27) also showed no significant relationships between BMD levels and serum ferritin, P, and PTH hormone ($p>0.05$). On the other hand, they delineated the significant correlations between both femur and spine BMD values with blood ALP and Ca parameters ($p<0.05$). Moreover, femur BMD value was significantly correlated with Vit D3 level ($p=0.04$). It should be noticed that the authors divided their participants into two groups of low and normal BMD values based on Z scores below and above -2.

The present study conducted at a referral center in Iran to show the prevalence of bone metabolic disorders and its risk factors; however, the study had several limitations. The main one was the small sample size. The population study had wide range of age distribution. Besides that, several blood biochemical (like hemoglobin and transferrin) and hormonal factors (such as gonadal, thyroid, and growth hormones) were not considered in the study that may possibly affect the results. Future longitudinal studies with a larger sample size and including more variables are suggested.

5. Conclusion

The findings of present study revealed that β-thalassemia patients are at great risk of bone metabolic disorders. Although the results showed no correlations between BMD levels and several blood biochemical factors, β-thalassemia major patients should be monitored for potential blood biochemical imbalance and their associated long-term consequences. It is supposed that providing protocols, patients' training, early intervention, and regular follow up may beneficially alleviate the risk of complications. Future studies with a larger sample size and including more factors are suggested.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

Statement of ethical approval

The present study was approved by the Ethical Committee of the Tehran University of Medical Sciences (ID:IR.TUMS.IKHC.1398.047) based on the Helsinki declaration.

Statement of informed consent

Written informed consent was given from the participants. All data were considered confidential and no extra cost was imposed to subjects regarding paraclinical examinations.

Availability of data and materials

The datasets related to our study are available from the corresponding author on reasonable request.

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