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Bone Mineral Density among adolescent's patients with β-thalassemia major.

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Abstract

Background: Beta-thalassemia is an autosomal recessive hemoglobinopathy with frequent skeletal complications, often debilitating in adolescent patients. We aim to evaluate the bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) and ascertain osteoporosis/osteopenia frequency in patients with β-thalassemia major.

Methodology: In this cross-sectional study, 36 adolescent patients with β-thalassemia major were enrolled from June 2015 to March 2017. BMD was measured in the anteroposterior lumbar spine (L1-L4) and femoral neck by DEXA. For the biochemical estimations, blood and urine samples were obtained and analyzed. The results of a bone density test were presented as T and Z scores.

Results: There were 20 male and 16 female patients with a mean age of 21.33 ± 3.7 years. The mean bone mineral content (BMC) was 20.10 ± 6.0 gm, and the mean BMD was 0.65 ± 0.07 gm/cm^2. The mean T score was -3.17 ± 1.04, and the Z score was -3.06 ± 1.06. All patients had low BMD, as depicted by their T or Z scores. The reported frequency of osteoporosis and osteopenia was 77.7% and 22.2%, respectively.

Conclusion: All Beta-thalassemia major patients had low BMD with a remarkable incidence of osteoporosis. It is recommended to perform an annual BMD among thalassemic patients to prevent fatal consequences and achieve an optimal bone density among such patients.

Keywords

Beta-Thalassemia Major, Bone Mineral Density, Osteoporosis, Osteopenia, Dual-Energy X-Ray Absorptiometry.

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Introduction

Beta-thalassemia, also called Cooley's anemia, is an inherited hemoglobinopathy, which is the most frequent genetic disorder globally[1]. Pakistan is located in the thalassemia belt; around 4000 to 9000 children are born with β-thalassemia major each year[2,3]. Herein, the carrier rate is 5 to 8%, with uniform distribution in all ethnic groups[3].

Internationally, blood transfusion and suitable iron chelation distinctly elongate the life expectancy among patients with thalassemia[4]. Conversely, in Pakistan, the expectancy is only ten years[5]. However, in survivor's quality of life is miserable with frequent siderotic and non-siderotic complications. The skeletal complications include osteopenia, osteoporosis, rickets, spinal defects, and spontaneous pathological fractures, frequently reported among thalassemic patients[6,7]. Contributing factors include expansion of medulla, iron deposition, calcium-phosphorus imbalance, rapid bone turnover, hormonal deficiency and hypoxia[8].

BMD is a good indicator of bone status, and it predicts the fracture risk among the patient population. According to the World Health Organization (WHO), osteoporosis is recognized based on the BMD T-Score, i.e. a score lower than -2.5 and the BMD T-score between -1 to-2.5 is indicative of osteopenia[9,10]. The WHO criterion has been widely accepted and provides both diagnostic and intervention threshold. DEXA is a paramount gold standard non-invasive test for the assessment of bone density. It measures BMD at the spine and hip, holding a significant role in the osteoporosis risk evaluation[8,11,12].

As locally, there is not much evidence on the role of DEXA in assessing fracture risk and the suitable anatomical site for assessment. Therefore, through this study, we aim to estimate the BMD in transfusion-dependent thalassemia patients and predict the fracture risk.

Methodology

Study Design & Subjects

In this cross-sectional descriptive study, 36 patients with transfusion-dependent thalassemia ≥18 years presenting at Liaquat National Hospital's hematology department were enrolled. The study extended from June 2015 to March 2017. All registered patients were on regular blood transfusion and parenteral iron chelation. Patients younger than 18 years, those with β-thalassemia intermedia and compound heterozygous were excluded from the study. Neither of the patients had any evident pathological fracture manifestations before or during the study period. Written informed consent was acquired from patients. The Institutional Ethical & Research Committee of Liaquat National Hospital & Medical College approved the study protocol.

BMD Evaluation

BMD was measured in the anteroposterior lumbar spine (L1-L4) and femoral neck through DEXA, performed on Hologic discovery Wi. Images of the left hip and the lumbar spine were acquired in the Posterior-Anterior (PA) projection. The data was analyzed by Hologic software version 13.3:5. The bone density test results were presented as DEXA T-score (DTS) and DEXA Z-score (DZS). Normal values of BMD were measured from 0.8 to 1.4 gm/cm^2. T-score was determined by comparing the patient's bone density with a normally expected healthy young individual of same-sex, and Z-score is the number of SD (standard deviation) from a normal individual with matching age, sex, weight and ethnic background. The normal value for T scores are ≥-1, and levels below were defined as abnormal. Low Z-score was defined as levels below -2.0. Osteoporosis and osteopenia were defined as per the World Health Organization (WHO) criteria.

Laboratory Assessment

The blood and urine samples were acquired for laboratory estimations. Hematological parameters were determined by automated analyzer Cell Dyne Ruby (Abbott, diagnostic). The Hitachi 912 instrument was used to evaluate liver function test, serum calcium, and phosphorus through

photometric assay, while immunoturbidity methodology was used to measure the serum ferritin level. Serum vitamin D was detected by Cobas e 411 analyzers (Roche, Japan) by chemiluminescence technique.

Fracture risk assessment using the FRAX Calculation

The probability of major osteoporotic and hip fractures was determined using FRAX[13]. Patients with ≥ 20% probability (10-year) for major osteoporotic fractures or ≥ 3% probability for hip fractures are at greater risk of attaining osteoporotic fractures than the counterparts.

Statistical Analysis

The collected data was analyzed using SPSS version 22.0. Mean with standard deviation was used to express quantitative variables. Categorical variables were summarized as percentages and frequencies. A Chi-square test was applied to assess the associations, where a p-value <0.05 was considered statistically significant.

Results

A total of 36 homozygous TM patients were included, with a mean age of 21.33 ± 3.7 (18–26) years. Gender distribution displayed a male majority (n=20). The observed hemoglobin level was 7.7 ± 2.9 gm/dL, with a hematocrit of 23.1 ± 5.7%. The mean total leukocytic count and platelets count of the patients was 7.5 ± 3.9 × 109/L and 158.7 ± 94.1 × 109/L, respectively. Serum ferritin levels were found to be markedly elevated. Moreover, other laboratory estimates, including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), calcium, phosphorus, 25-OH vitamin D, total, direct and indirect bilirubin levels were also assessed, and the results are presented in Table 1. Hypocalcemia and hypophosphatemia were observed among 66.6% and 16.6% of the patients, respectively, while 72.2% had 25-OH vitamin D deficiency.

Table 1: Demographic and Laboratory Characteristics

Variables		Mean ± SD
Age (years)		21.33±3.7 (Range: 18–26)
BMI (kg/m^2)		21.6±10.3
Gender n(%)	Male	20(55.5)
	Female	16(44.4)
Laboratory findings	Hemoglobin (gm/dL)	7.7±2.9
	Hematocrit (%)	23.1±5.7
	Leukocyte Count × 10^9/L	7.5±3.9
	Platelets Count × 10^9/L	158.7±94.1
	Ferritin (ng/ml)	4599.7±3029
	Total Bilirubin (mg%)	1.5±0.8
	Direct Bilirubin (mg%)	0.5±0.5
	Indirect Bilirubin (mg%)	0.9±0.5
	Serum ALT (U/L)	70.5±71.7
	Serum AST (U/L)	69.0±40.7
	Calcium	8.1±0.8
	Phosphorus	3.1±1.2
	25(OH)D (ng/mL)	22.1±8.7

*ALT-Alanine Aminotransferase; AST-Aspartate Aminotransferase

The DEXA profile showed that the BMD in the enrolled population was collectively low. The mean BMD was 0.65 ± 0.07 gm/cm^2 with the mean T score of -3.17 ± 1.04 and the Z score of -3.06 ± 1.06. Of the total, 28(77.7%) patients were osteoporotic, while 8(22.2%) had osteopenia. No statistically significant difference was noted between genders (p>0.05).

Table 2: Dual-energy X-ray absorptiometry profile

DEXA profile (Mean ± SD)	BMC (gm)	20.10±6.0
	BMD (gm/cm^2)	0.65±0.07
	DTS	-3.17±1.04
	DZS	-3.06±1.06

*DTS-DEXA T-score; DZS- DEXA Z-score

According to the WHO Fracture Risk Assessment Tool (FRAX), the ten-year probability of a major osteoporotic fracture and hip fracture risks was 15.4% and 13.7%, respectively. No correlation was ascertained between low BMD and vitamin D deficiency or hypocalcemia, as all patients had low BMD.

Discussion

Significantly reduced BMD was observed among the enrolled transfusion-dependent β-thalassemic patients. As per the WHO criteria, osteoporosis was frequent, i.e. 77.7%. Despite therapeutic improvements in management strategies, it has been anticipated that 60 to 90% of thalassemic patients have osteopenia or osteoporosis[9]. Our findings are intermediate with other studies indicating that osteoporosis prevalence is 27- 89% among thalassemic patients[14-16]. A similar local Pakistani study determined osteoporotic frequency among thalassemic patients as 47.3%[17].

An early diagnosis of low BMD is suggested to improve the quality of life and avert its complications15. Similarly, bone density was also lowest in 9 to 18 years old Lebanese β-TM patients (n=29) than the healthy matched controls[18]. There was no statistically significant difference between genders regarding BMD in our study. Similarly, Shamshirs et al. and Karimi et al. from Iran have shown no significant difference in osteoporosis prevalence between males and females[19,20]. Contrary to our finding, Jensen et al. determined more bone changes in males than in females (p=0.04)[21].

According to this study, the mean T-score was -3.17 ± 1.04, and the mean Z-score was -3.06 ± 1.06. None of the enrolled patients had normal T or Z scores. A recent study from Egypt by Nawar et al. has shown the mean Z score of -1.5 ± 1.2 in the patient group versus -0.2 ± 0.9 in the control group (p<0.001)[22]. Previous reports showed a strong association between low bone mass and pathological fractures, and it is well-identified factors that contribute to the bone deformities in thalassemia[23].

It is of consideration that none of our patients had fractures though some of them had complaints of intermittent pain. The fracture prevalence was relatively high (36%) in a large cohort of 372 patients from the USA[23]. Our findings differed from the TCRN report, which observed an overall fracture prevalence of 12% in thalassemic patients[24]. This difference could be attributed to the small sample size in our study and is unlikely to reflect our population's actual prevalence. Hence, the findings of the current research need to be validated in a large cohort of patients.

Thalassemia International Federation recommends annual assessment of BMD in transfusion-dependent thalassemia patients, starting from adolescence[25]. However, the availability and, more notably, affordability of DEXA scanning are a major limitation in developing nations. There are certain limitations to the present study; the small number of patients and a control group for comparison are the major ones. We recommend that future studies in Pakistan be pursued on a large sample size to address these confounders and include a control group for comparison.

Conclusion

The prevalence of osteoporosis and osteopenia among adult thalassemia patients was relatively high. BMD is a useful index for assessing bone status among patients with thalassemia and is recommended to be done annually in thalassemic patients. Early diagnosis will prevent fatal

consequences of osteoporosis due to timely and appropriate management.

Conflicts of Interest

None.

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