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ORIGINAL ARTICLE

Thalassemia and the skeletal system; a clinical and radiological analysis

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ABSTRACT

Background: Thalassemia can lead to various skeletal complications due to the effects of chronic anemia and iron overload. Common pathologies include bone deformities, osteoporosis, and fractures, particularly in the skull, long bones, and spine. Iron deposition in bones, coupled with abnormal bone marrow expansion, contributes to skeletal abnormalities. A comprehensive understanding of these skeletal manifestations is essential for improving management strategies and minimizing morbidity in thalassemia patients.

Methods: It was an observational case control study and was hospital based, executed at department of Hematology mainly in collaboration with Medicine, Radiology and Pathology departments of (RYK Hospital, Rahim Yar Khan). Commencement of study took place on 12th of March 2022 and concluded on 11th of June 2023. Forty (40) patients and forty (40) controls participated in study. The data obtained was scrutinized by statistical package for social sciences software (SPSS) version 24. Dual-Energy X-ray Absorptiometry (DEXA) scans were generated for every case and control.

Results: Our research found that people suffering from thalassemia have increased risk of weaker skeletal framework by -11.160 times at anatomical neck of femur and -6.670 times at vertebrae (lumbar) in comparison to controls. Cases versus control comparison of bone mineral density (BMD) also revealed a statistically highly significant difference also.

Conclusion: in light of our results, there is highly significant evidence that well above the half of the patients affected by thalassemia has weaker bones and should be evaluated and treated frequently for skeletal pathologies.

Keywords: DEXA Scan, Osteoporosis, Osteopenia, Thalassemia,

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Introduction

Thalassemia is a genetically inherited disease characterized by a diminished or completely no synthesis of globin chains. One or more mutations in globin chains (Beta) results in Beta-thalassemia and it in turn leads to anemia due to ineffective erythropoiesis (1).

Lowered mass of bone is frequently prevailing problem. Despite sufficient blood transfusion and iron therapy, transfusion-dependent thalassemia has arisen as a significant concern impacting both children and adolescents (2). Low bone mass can be caused by a number of conditions, such as iron deposition, medulla enlargement, hormone deficiencies, fast bone turnover, calcium and phosphorus imbalance, and lack of oxygen. Due to the severe anemia caused by the homozygous condition of the illness, more blood transfusions are eventually needed (3). The patient's life expectancy has been greatly extended by the current thalassemia major care, which entails frequent transfusion therapy and concomitant iron chelation therapy (4). Unfortunately, there is now a higher chance of difficulties due to this longer lifespan. Due to iron excess, thalassemia is linked to a number of issues that affect several organs, including the parathyroid, pituitary, thyroid, pancreas, gonads, and bone (5). Fractures, osteopenia, osteoporosis, discomfort, bone deformities, and marrow enlargement are all caused by low bone mass (6). Well documented fact is that children who require transfusions frequently have poor bone mass. Nevertheless, limited research has demonstrated that individuals with non-transfusion-dependent thalassemia may also experience reduced bone mass in their later years. It is commonly known that thalassemia patients frequently have inadequate bone density (7). Nevertheless, there are surprisingly few researches looking at how thalassemia patients' bone mineral density (BMD) varies. Therefore, the aim of study focused to gain a better knowledge of the numerous clinical variables associated with lowered bone mass in adolescents suffering from thalassemia and its prevalence. Results of this study will increase knowledge about this illness, resulting in early diagnosis and efficient treatment.

Methods

The purpose of this hospital-based observational case-control research was to analyze bone mineral density (BMD) using bone densitometry and characterize clinico-pathological composition of thalassemic patients. After approval from the appropriate Institutional Ethics Committee with reference number IERC/SZMCH/02/2022/01-012 dated March 11, 2022, the study was carried out for fifteen (15) months, from March 12, 2022, to June 11, 2023, in the department of Hematology in association with Medicine and Radiology at Sheikh Zayed Hospital & Medical College in cooperation with RYK Medical College and Hospital, Rahim Yar Khan. Every participant of the study submitted informed consent prior to commencement of study. After screening, patients with thalassemia were chosen among those enrolled in the hematology or medicine departments. Total numbers of forty (40) cases were included in the research, with a male to female ratio of 1:1. Additionally, forty (40) from the staff and attendees, healthy control participants were randomly selected, ensuring that the gender ratio remained equal and overall sample size became eighty (80). Patients with any accidental or surgical history, any systemic disease like myocardial infarction, renal failure, chronic liver disease, stroke, critical illness and also females with menorrhagia and patients who were not willing to join despite informed consent were excluded from the study. Clinstat an online statistical calculator was used to calculate sample size (www.clinstat.eu) in addition to manual calculation as per the formula given below.

With 95% confidence interval, a sample size of 80 was declared satisfactory, for manual calculation of sample size following formula was used (8, 9).

$$(n) = \frac{(r+1)p(1-p)\left(Z_{1-\beta}+Z_{1-\frac{\alpha}{2}}\right)^2}{r(p_1+p_2)^2}$$

(n) = Sample size, r = Ration of case to control, p = Population proportion, p_1= Case proportion, p_2 = Control proportion, $Z_{1-\beta}$ = Power of study, $Z_{1-\alpha/2}$ = Critical value

At the lumbar spine (LS) (L2–L5) and the neck of the femur (NF), bone mineral density (BMD) was analyzed by dual-energy X-ray absorptiometry (DEXA) with DXA 800F – Pinyuan (China). Every subject's data were documented and presented as the absolute value (gram/cm2) of the BMD of the LS and NF. Osteoporosis was defined in this study as having Z score $\leq -2.5 \pm$ standard deviation (SD), whereas osteopenia was defined as having a Z score between −1 and −2.5 standard deviation (SD). Men and children are not covered by the World Health Organization's (WHO) description of osteoporosis, which solely pertains to puberty attained women. This is mostly because there is little evidence of a link between decreased bone mass and associated fractures in childhood, and the association in postmenopausal women is clearer than it is in males. Z scores are preferable in males under 50 years old and in females prior to menopause (10). The numerical variation of standard deviations below or above mean value is represented by a Z score, which is how we reported the BMD results. The Z Scores have been used in many researches to classify osteopenia and osteoporosis (11- 13). Therefore, we defined a Z score between −1 and $-2.5 \pm$ S.D for osteopenia and a Z score < $-2.5 \pm$ S.D for osteoporosis in our study. Excel by Microsoft (2018) as well as statistical package for social sciences (SPSS-24 from Microsoft Incorporation) was utilized to do the data's statistical analysis. Whereas discrete data was reported with numbers and percentage (%) as well as examined by applying Chi-square test, continuous measurement results were shown with mean ± standard deviation, in addition independent t-test was applied for comparison. A 5% standard of significance with ($P < 0.05$) was marked for statistical evaluation.

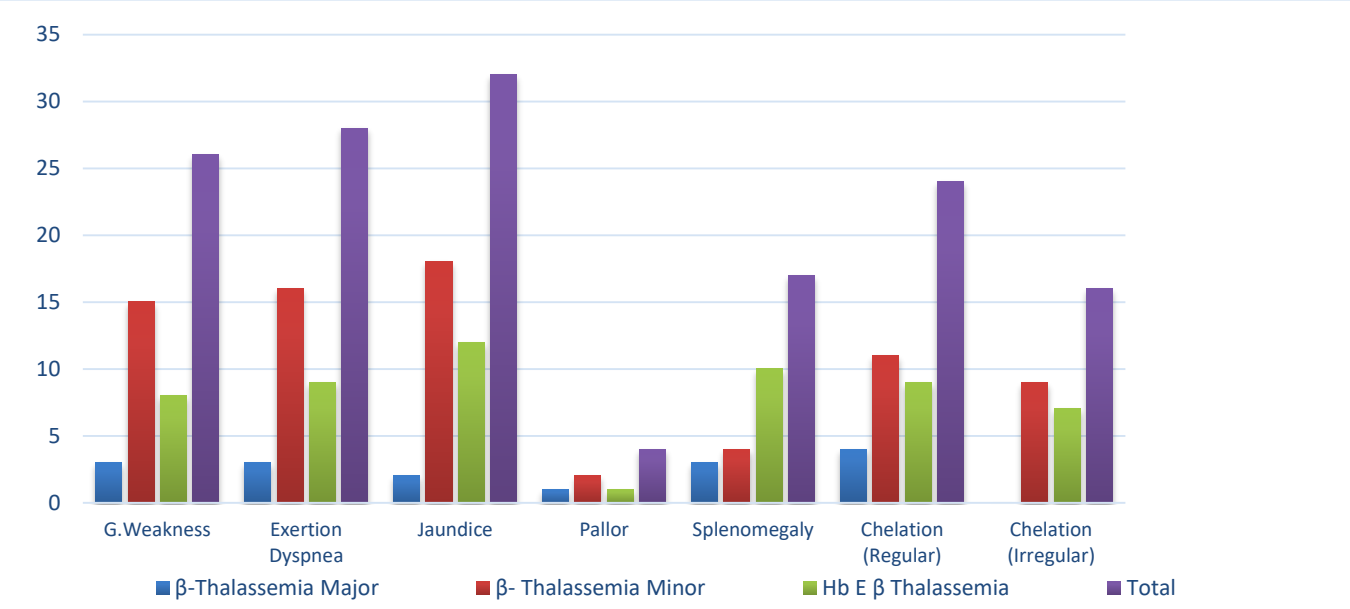
Results

Referring to table 1 describes the age distribution of 80 individuals, evenly divided between cases and controls, with an equal gender ratio (1:1). It focuses on three forms of thalassemia: β-thalassemia major, β-thalassemia minor, and Hb E β-thalassemia. The participants are divided in four groups according to age (1-9, 10-18, 19-27, and 28-36 years). The highest percentage of individuals (37.5%) falls in youngest age group (1-9 years), secondly 30% in 10-18 age group. The largest number of cases in these groups is of β-thalassemia minor and Hb E β-thalassemia, while β-thalassemia major is less frequently observed. A very small number of cases were in the 28-36 age range (10%). The mean diagnostic age of overall groups is around 2.9 years, indicating that diagnosis frequently occurs at very young age, with some variation across the age groups. (Table -1)

Table 1: Age distribution (n=80) Cases & Controls ratio 1:1, Gender ratio 1:1

Age group	B - thalassemia major (n=40)	B - thalassemia minor (n=40)	Hb E β - thalassemia(n=40)	Total	Mean Diagnostic Age (years)
1-9	02	05	08	15(37.50%)	2.5 ± 1.25
10-18	02	06	04	12(30%)	2.7 ± 1.39
19-27	00	05	04	09(22.5%)	3.1 ± 1.11
28-36	00	04	00	04(10%)	3.2 ± 1.37
Total	04	20	16	40	2.9. ± 1.32

Analysis of different patterns of clinical signs and symptoms across three types of thalassemia (β-thalassemia major, β-thalassemia minor, and Hb E β-thalassemia) showed that the most common symptoms, with over 30 cases for each symptom, are more common in people with Hb E β-thalassemia, including generalized weakness, exertion associated dyspnea, and jaundice. Comparatively, β-thalassemia major has the fewest cases in all categories, while β-thalassemia minor exhibits moderate levels of these symptoms. About fifteen people with Hb E β-thalassemia also have splenomegaly, or an enlarged spleen, whereas pallor is less common in all forms. Chelation therapy, either regular or irregular is more commonly used in Hb E β-thalassemia. All things considered, Hb E β-thalassemia is the type that affects the greatest number of people in most categories. (Figure – 1)



In lumbar spine (LS) and femoral neck or the neck of femur (NF), radiologic anatomy analysis using Dual Energy X-Ray Absorptiometry (DEXA) was performed for comparison of Bone Mineral Density (BMD) between 40 patients and 40 controls showed that a significantly higher percentage of patients have low BMD compared to controls. Compared to 52.50% of controls, 92.55% of patients in the lumbar spine had osteopenia or osteoporosis. Patients were more likely to have osteoporosis than controls; 50% of patients and controls, respectively, had osteoporosis. Additionally, a p-value of 0.000 and odds ratio of -11.160 show that, difference is statistically highly

significant. In the same way, 80% of patients and 37.50% of controls, respectively, had lowered bone mineral density (BMD) in femur neck (odds ratio: -6.670, p-value: 0.000). While osteoporosis was found in 25% of patients and only 7.50% of controls, osteopenia affected 55% of patients and 30% of controls. Patients' mean BMD values were lower in both regions: patients' lumbar spine BMD was 0.941 g/cm² compared to controls' 0.788 g/cm², and patients' neck of the femur BMD was 0.799 g/cm² compared to controls' 0.994 g/cm². Both differences had significant p-values of 0.001. These results imply that compared to controls, patients have a much higher likelihood of having decreased bone density. (Table – 2)

Table -2: Radiologic Anatomy Analysis using Dual Energy X-Ray Absorptiometry (Dexa)

Measurements	Patients (n=40)	Patients %	Controls (n=40)	Control %	Odds ratio (OR)	P-Value
Bone Mineral Density (BMD) Lumbar Spine (LS)						
Osteopenia	17	42.50%	13	32.50%	×	×
Osteoporosis	20	50.00%	8	20.00%		
Total low BMD	37	92.55%	21	52.50%	-11.160	***0.000****
Bone Mineral Density (BMD) Neck of Femur (NF)						
Osteopenia	22	55.00%	12	30.00%	×	×
Osteoporosis	10	25.00%	3	7.50%		
Total low BMD	32	80.00%	15	37.50%	-6.670	***0.000****
Mean Bone Mineral Density (BMD) ± Standard deviation (LS & NF) g/cm²						
Lumbar Spine	0.941 ± 0.231	×	0.788 ± 0.175	×	×	***0.000****
Neck of Femur	0.799 ± 0.201		0.994 ± 0.248			***0.000****

Discussion

Compared to normal, healthy controls, the results indicate that adolescents with thalassemia have increase in prevalence of lowered BMD. The large number of the cases in our experiment had generalized weakness, exhaustion, and dyspnea upon exertion. In addition, pallor, icterus, splenomegaly, and hepatomegaly were noted. These signs and symptoms are comparable to those reported in studies by Nakavachara P et al, which showed that nearly all of the cases had generalized weakness and exhaustion (14). Unreliable chelation therapy and insufficient blood transfusions can both cause clinical manifestation. Once more, even repeated transfusions can result in an iron overload condition in multiple organs, which can define symptomatically as hypogonadism, pancreatitis, thyroidal deficiency, parathyroid hormone deficiency and similar endocrine issues as well as cardiomyopathy, hepatic fibrosis and cirrhosis. These are common feature with Atmakusuma TD et al (15).

Thirty-seven (92%) of the forty patients whose BMD was measured at LS using a DEXA scan had low BMD. In other words, 20 patients (50.00%) had osteoporosis and 17 patients (42.50%) had osteopenia. While 8(20.00%) and 13(32.50%) of the controls had osteopenia and osteoporosis, respectively, and 21(52.50%), just slightly more than half, had low BMD. These results show statistical significance (p-value = 0.000) and are consistent with the observations made by Wiromrat P et al who reported regarding bone mineral density in lumbar spine cases: in normal range (17.1%), osteoporosis (48.6%) and osteopenia (34.3%) (16). Similar findings

were found at LS in another study by Charoenngam N et al who reported 20% with adequate bone mineral density, 37.5% with osteopenia and 42.5% suffering from osteoporosis (17). However, a different study results were documented by Gaudio A et al who found that the LS in cases had an insignificantly low prevalence of osteoporosis and osteopenia, at 10.5% and 11.6%, respectively (18).

Only 8 cases (20.00%) at the femur neck were found to have normal BMD, while 25 individuals (62.50%) in the control group did. Twenty-two (55.00%) of the forty cases had osteopenia; twelve (30.00%) of the cases in control were also possessing osteopenia. Osteoporosis was present in 10 (25.00%) of the cases, compared to 3 (7.50%) in the control group. We found statistically highly significant result in bone mineral density with a value of ($P < 0.000$) between the cases and controls; similar results had been documented by the work performed by Ananvutisombat N et al (19). 92.55% (37 out of 40) of the cases in our study had bone involvement at LS, compared to 52.50% (21 out of 40) of the controls. The computed odds ratio, -11.160, confirms that, in comparison to a normal, healthy population the thalassemia cases have11.160 times higher chance of decreased bone mineral density at lumbar spine having odds ratio (OR – 11.670, $P = 0.000$). Correspondingly, while comparing bone mineral density at the neck of the femur it was evident from results that thalasemic cases had 6.670 times increased chance of having lowered bone mineral density (OR - 6.670, $p = 0.000$) in comparison to their counter controls. These results are extremely similar to those reported by Das A et al (20). Thus, our research clearly shows that, in comparison to normal populations, individuals with thalassemia have a greater chance to suffer from osteopenia and osteoporosis, which is consistent with majority of the previous studies mentioned.

Low BMD is also caused by large number of other conditions, such as hypogonadism, vitamin D insufficiency, and aberrant GH-IGF-1 axis. However, budgetary constraints prevented us from performing tests that would have given us more information on the subject, including those measuring calcium, phosphorus, parathyroid hormone, and vitamin D3. It's submitted that the sample size of study was somewhat limited; nonetheless, in order to gain a deeper understanding of the variables influencing BMD changes in thalassemia patients, greater sample sizes and longer study periods are required.

Conclusion

According to this study, osteoporosis and osteopenia were the most prevalent types of decreased bone mineral density (BMD) among the half of Thalassemia patients. Patients with Thalassemia had greater effects on the FN and LS than controls did. These results emphasize the necessity of routinely assessing and treating skeletal pathologies in patients suffering from thalassemia in order to stop the emergence of major problems.

Conflicts of interests: All authors unanimously declare - no conflicts of interests.

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