JRMI
Journal of Rehman Medical Institute

Volume 10, No. 3
July - September 2024
www.jrmi.pk

ORIGINAL ARTICLE

Osteoporosis in adult thalassemia major patients presenting at a tertiary care hospital

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Submitted
July 14, 2024
Accepted
August 30, 2024

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Citation: Khalid M, Khattak M, Tariq M, Haq M, Mufti MZ, Malik SN. Osteoporosis in adult thalassemia major patients presenting at a tertiary care hospital. J Rehman Med Inst. 2024 Jul-Sep;10(3):16-20.

ABSTRACT

Background: Thalassemia, the most globally prevalent inherited hemoglobinopathy, poses significant health complications, including osteoporosis, which affects up to 50% of patients, regardless of gender. As lifelong transfusions remain a common treatment due to the risks associated with stem cell transplantation, this study seeks to provide updated insights to guide diagnosis, management, and future research.

Objective: To determine the magnitude of Osteoporosis in adult thalassemia major patients attending a tertiary care hospital of Peshawar.

Methodology: This cross-sectional study was conducted in Department of Hematology, Hayatabad Medical Complex, Peshawar, over six months from June 22, 2021, to December 22, 2021. All the included patients were subjected for bone mineral density test for the diagnosis of osteoporosis. Bone mineral density test was conducted by an expert radiologist. Osteoporosis was considered positive if the bone mineral density or T-score was less than -2.5. Data were analyzed using SPSS version 22, with the Chi Square test employed for any association, and $p \leq 0.05$ considered significant.

Results: This study of 139 thalassemia patients revealed that average age was 27 years±1.88. About 48.9% (n=68) aged 18-25years and a male-to-female ratio of 1.4:1. Additionally, 44%(n=61) had diabetes mellitus, 37%(n=51) were obese, and 21%(n=29) had osteoporosis. Notably, osteoporosis prevalence was significantly associated with a positive family history of thalassemia (p=0.032), but no association was seen with age, gender, diabetes, or obesity.

Conclusion: According to the study's findings, 21% of thalassemia major patients who presented to tertiary care hospitals had osteoporosis. Nutritional support and deficiency prevention are essential to lowering the burden of issues and enhancing the quality and duration of life for TM patients.

Keywords: Osteoporosis; Thalassemia Major; Bone Mineral Density; β-thalassemia.

The authors declared no conflict of interest. All authors contributed substantially to the planning of research, data collection, data analysis, and write-up of the article, and agreed to be accountable for all aspects of the work.

INTRODUCTION

Thalassemia, the most prevalent inherited hemoglobinopathy globally, often necessitates lifelong transfusions for patients, given the risks associated with stem cell transplantation.[1,2] Thalassemia Major (TM) presents with severe anemia, jaundice, and enlarged organs in infants. Thalassemia Intermedia shows milder symptoms later in life, while carriers may have mild anemia or be asymptomatic.[3] Thalassemia is prevalent worldwide, affecting millions of individuals.[4] In Pakistan, β-thalassemia is one of the most common inherited disorders.[5]

The pathophysiology of thalassemia is intricate and involves both intracellular processes and their systemic consequences. Regarding β-Thalassemia, the primary defect is the diminished or absent production of β-globin chains; in α-thalassemia, there is an imbalance in globin biosynthesis, resulting in excess β-, γ-, or both globin chains.[6] Recent advancements in molecular biology and the widespread availability of DNA analysis methods have facilitated the identification of globin gene defects in thalassemia, shedding light on the mechanisms of globin gene regulation and expression. Distinguishing between thalassemia major and intermedia is crucial for tailoring appropriate treatment strategies.[7] Silent Carrier are often asymptomatic, while Hemoglobin H Disease (HbH Disease) and Hb Bart Hydrops Fetalis Syndrome are most severe α-thalassemia condition, typically associated with absent function of all four α-globin genes (homozygous α0-thalassemia or -/-).[8]

Osteoporosis is prevalent in both genders with thalassemia, affecting up to 50% of patients.[9] The imbalance between osteoclastic resorption and osteoblastic formation leads to bone loss.[10] Thalassemia Major (TM) arises from faulty globin synthesis, leading to abnormal and reduced globin chains, ineffective erythropoiesis, and increased red blood cell turnover. Despite improved treatment, osteoporosis and osteopenia persist as significant complications in TM patients.[9] Bone marrow expansion, despite regular transfusions, contributes to bone destruction in TM, possibly by stimulating osteoclast formation. Iron overload, primarily in endocrine glands, leads to various endocrine dysfunctions, including growth failure

and hypogonadism, exacerbating bone loss. Iron deposition in bone and the use of deferoxamine for iron overload treatment negatively impact bone health. Vitamin D deficiency, common in TM patients, further contributes to osteoporosis.[11] Genetic factors, including polymorphisms in COL1A1, TGF-β1, and VDR genes, influence Bone mineral density (BMD) in TM patients.[12] In summary, TM-associated osteoporosis results from complex interactions between genetic predisposition, hormonal imbalances, iron overload, vitamin deficiencies, and dysregulated bone metabolism pathways.[13] Understanding these factors is crucial for developing effective management strategies for bone health in TM patients. Findings will aid healthcare professionals in diagnosis, management, and future research on thalassemia-related osteoporosis. This study aims to provide current data on osteoporosis frequency in thalassemia major patients, lacking in our population for the past five years.

MATERIALS & METHODS

The study was conducted after approval from hospitals ethical and research committee. A written informed consent was obtained from the parents.

This descriptive cross-sectional study conducted at the Department of Hematology, Hayatabad Medical Complex, Peshawar, spanned 6 months from June 22, 2021, to December 22, 2021. Employing consecutive (non-probability) sampling, 139 participants were enrolled based on a World Health Organization (WHO) sample size calculator with keeping 36.1% prevalence of osteoporosis[14] in adult thalassemia major patients with 95% confidence level and 8% margin of error.

The inclusion criteria encompassed patients aged 18-60 years with thalassemia major of more than 6 months duration, irrespective of gender. Already diagnosed cases of osteoporosis in thalassemia major, patients having conditions such as acute and chronic inflammatory diseases, infections, hypothyroidism, acute bleeding and any kind of malignancy that may alter the level of ferritin and hemoglobin, and patients with bleeding disorders as diagnosed on history and medical records were excluded from the study.

A detailed history was taken, clinical examination was done, and laboratory investigations were performed for confirmation of thalassemia major. All the included patients were subjected for bone mineral density test for the diagnosis of osteoporosis. Bone mineral density test was conducted by expert radiologists who had at least 2 years of experience. Osteoporosis was considered positive if the bone mineral density (BMD) scores (T-score) was less than -2.5. All the above-mentioned information including age, gender, weight, height, BMI, serum ferritin levels, diabetes mellitus, obesity, family history thalassemia major was recorded on a pre-designed proforma.

All the data were analyzed in statistical software SPSS version 22. Mean and standard deviation were calculated for continuous variables like age, weight, height, BMI, serum ferritin levels. Frequencies and percentages were computed for categorical variables like gender, diabetes mellitus, obesity, family history thalassemia major, osteoporosis. Osteoporosis was stratified among age, gender, diabetes mellitus, obesity, and family history of thalassemia major to see the effect modifications using Chi Square test, where p value ≤0.05 was considered as significant.

RESULTS

The age distribution of the patients in the current study was examined; 48.9% were between the ages of 18-25 years, followed by 26-35 years with 25.9%, 36-45 years with 15.1%, and 46-55 years with 10.1%. Analysis of the gender distribution revealed that 57(41%) of the patients were female and 82(59%) of the patients were male (Table 1).

Table 1: Age and gender distribution of patients (n=139).

Variables		Frequency (%)
Age Groups (years)	18-25	68 (48.9)
	26-35	36 (25.9)
	36-45	21 (15.1)
	46-55	14 (10.1)
	Total	139 (100.0)
Gender	Male	82 (59%)
	Female	57 (41%)
	Total	139 (100%)

Analysis of the patients' diabetes mellitus status revealed that 61(44%) had the disease and 78(56%) did not. Analysis of the patients' obesity status revealed that 51(37%) were obese and 88(63%) were not (Table 2).

Table 2: Status of Diabetes Mellitus and Obesity (n=139).

Variables		Frequency (%)
Diabetes Mellitus	Yes	61 (44%)
	No	78 (56%)
	Total	139 (100%)
Obesity	Obese	51 (37%)
	Non-obese	88 (63%)

The mean BMI was 27 ± 3.11 kg/m^2, mean weight was 82 ± 10.72 kg, & mean height was 1.5 ± 0.94 m.

Analysis of the patients' family histories revealed that 125(65%) patients had a negative family history of thalassemia, while 14(10%) patients had a positive family history.

The status of osteoporosis showed that 29 (21%) patients had osteoporosis, and 110(79%) patients did not have osteoporosis (Table 3).

Table 3: Family History of Thalassemia and Status of Osteoporosis (n=139).

Variables		Frequency (%)
Family History	Positive	14 (10%)
	Negative	125 (90%)
Osteoporosis	Yes	29 (21%)
	No	110 (79%)

Stratification of osteoporosis with respect to age groups is shown in Table 4.

Table 4: Frequency of Osteoporosis based on age groups (n=139).

Variables		Osteoporosis f(%)		
		Yes (n=67)	No (n=72)	Total (n=139)
Age Groups (Years)	18-25	56 (83.6)	12 (16.7)	68 (48.9)
	26-35	0 (0%)	36(50)	36(25.9)
	36-45	11 (16.4)	10 (13.9)	21 (1.5)
	46-55	0 (0%)	14 (19.4)	14 (1.0)

Out of the 67 patients with osteoporosis, the majority 56(83.6%) belonged to the age group of 18-25 years, with the remaining 11(16.4%) being the 36-45 years age group. By comparison, patients without osteoporosis were distributed in all the age groups, the majority 36(50%) being in the age group of 26-35 years.

Table 5 displays the stratification and association of Osteoporosis with gender, diabetes mellitus, obesity, and family history of thalassemia major. All variables showed non-significant associations except for a history of thalassemia which showed a significant association (p=0.0327).

Table 5: Association of Osteoporosis with gender, diabetes mellitus, obesity, and history of thalassemia (n=1139).

Osteoporosis	Gender		Total	p value
	Male	Female		
Yes	17(21%)	12(21%)	29(21%)	0.9634
No	65(79%)	45(79%)	110(79%)	
Total	82(100%)	57(100%)	139(100%)	
Osteoporosis	**Diabetes Mellitus**		**Total**	
	Yes	No		
Yes	13(21%)	16(10%)	29(21%)	0.9084
No	48(79%)	62(79%)	110(79%)	
Total	61(100%)	78(100%)	139(100%)	
Osteoporosis	**Obesity**		**Total**	
	Obese	Non-Obese		
Yes	11(22%)	18(20%)	29(21%)	0.8761
No	40(78%)	70(80%)	110(79%)	
Total	51(100%)	88(100%)	139(100%)	
Osteoporosis	**History of Thalassemia**		**Total**	
	Positive	Negative		
Yes	6(43%)	23(18%)	29(21%)	0.0327
No	8(57%)	102(82%)	110(79%)	
Total	14(100%)	125(100%)	139(100%)	

DISCUSSION

The most prevalent inherited hemoglobinopathy in the world is thalassemia. Patients with B-thalassemia major may choose to treat themselves with a lifetime regimen of transfusions to maintain growth and development and to enhance their quality of life, given the risks associated with hematopoietic stem cell transplantation.[15] On the other hand, the body's long-term accumulation of iron from transfusions can be fatal, affecting the liver, heart, and endocrine system. Deferoxamine (DFO), the first iron-chelating agent, was released in 1962. Since then, it has been successfully utilized to both prevent and treat complications related to iron overload.[16]

According to our analysis, out of 139 patients, 99(71%) were between the ages of 18 and 30 years, and 40(29%) were between the ages of 31 and 60 years; the mean age was 27±10.88 years. Of the patients, 57(41%) were female and 82(59%) were male. Thalassemia major is found in males more frequently as compared to females.[17] Seventy eight (56%) patients did not have diabetes, while 61(44%) patients did. Eighty eight (63%) patients were not obese, and 51(37%) patients were obese. A positive family history of thalassemia was present in 14(10%) cases, whereas a negative family history was present in 125(65%) patients. Osteoporosis was present in more than 29 individuals (21%) and not in 110 patients (79%). A recent study conducted by Baghersalimi et al.,[18] shows that osteoporosis was found in 12.4% individuals. Other studies reported frequently fractures of different body bones statistically significantly in thalassemia patients.[19,20] Common bone fractures reported in beta thalassemia patients was 17% as compared to alpha thalassemia with 4%.[20] A study reported 12/64 thalassemia patients with osteoporosis complication.[19] A study from Turkey reported by Celik et al.,[21] detected 10 out of 38 (26.3%) patients with osteoporosis in which 7 were males and 3 were female patients. Another study from Thailand by Thavonlun et al.,[9] revealed high prevalence of osteoporosis with 38.4% in transfusion dependent thalassemia

patients. Another study from Pakistan reported by Akram et al.,[22] which revealed highest percentage of osteoporosis in children and adolescent at 57.3%. Hashemieh et al.,[23] reporting from Iran also showed high prevalence of osteoporosis of 65.6% in thalassemia patients. Origa et al.,[24] also reported 48% osteoporosis from Italy. The dissimilarity might be due to regional and age differences of the population studied. Moreover, this difference between other studies and present study percentages could be due to sample size, or socioeconomical and cultural difference. Health care facilities, diagnostic services and management strategies are also important factors.

In a different study by Zadeh et al.,[14] 280 patients were referred to the nuclear medicine department for an osteoporosis assessment by DEXA test; of these, 136 were male and 144 were female; thalassemia major patients were 265(94.6%) and thalassemia intermedia 15(5.4%), with a mean age of 23.1±7.5 years (range of 11-45 years), and a mean BMI of 21.7±4.6; the prevalence of osteoporosis and osteopenia in various parameters like age group, nationality, gender, and thalassemia type were observed. Their data showed that the overall prevalence of osteoporosis was 36.1% (101 out of 280), with pediatric cases accounting for 43(42.6%) and adults for 58(57.4%), while the prevalence of osteopenia was 47.1% (132 out of 280), with pediatrics accounting for 53(40.2%) and adults for 79(59.8%); 47(16.8%) were reported as normal BMD results. The incidence of osteoporosis in women was 40.3%, but the prevalence rate in men was 43 (31.6%). Body mass index (BMI) and hemoglobin level were shown to be statistically significantly correlated with osteoporosis, but only nationality was found to be statistically significantly correlated with osteopenia patients. Similar findings were noted in a different study by Moradvaeisi et al.,[25] where the patients' mean age was 19.8±7.7 years, 24 of them (52.2%) were female, and 32 of them (69.6%) were older than 15 years old. The most common densitometry findings in this investigation were normal lumbar spine (34.8%) and osteoporosis (34.8%). Different amounts of ferritin were found in these individuals when the chemical biomarkers and femoral head densitometry results were compared (p=0.011). Patients with osteoporosis and normal densitometry data showed this difference (p=0.009).

Similar findings were found in different research by Hashemieh et al.,[26] where 214 out of 326 (65.6%) individuals had osteoporosis. In the lumbar spine alone (L1-L4), femoral neck alone, and both locations, osteoporosis was found in 10.7%, 11%, and 43.9% of patients, respectively. Of the remaining individuals, only 15.7% had normal values and 18.7% had osteopenia. Patients with thalassemia intermedia had a higher prevalence of osteoporosis in comparison to those with thalassemia major (p<0.001). Additionally, there was a favorable link found between osteoporosis and patient age, transfusion length, and intervals between transfusions. In conclusion, Iranian thalassemia patients have an osteoporosis prevalence that is comparable to that found abroad. Bone mineral density testing is advised for thalassemic patients on a yearly basis since it serves as a reliable indicator of bone health in these individuals. Beta-thalassemia patients with osteoporosis can be managed with calcitonin, zinc supplementation, bisphosphonates, calcium, and hydroxyurea.[27]

Similar findings were noted in another research by Ishaq et al.,[28] in which 42 patients (28%) were reported as being between the ages of 9 and 10; the study's mean age was determined to be 8.23+2.6 years. There were 70(46.67%) females and 80(53.33%) males. Children with beta thalassemia major had reduced bone mineral density in 73(49%) children, and osteoporosis in 71 (47.33%).

This study highlighted the significance of maintaining a normalized hemoglobin level, routinely measuring parathyroid hormone, closely monitoring growth parameters, and treating iron overload with the best possible iron chelation treatment.

LIMITATIONS

This study has several limitations that should be acknowledged. The relatively small sample size, cross-sectional design, and single-center focus may restrict the generalizability of the findings.

RECOMMENDATIONS

Future research should prioritize enrolling larger sample sizes that encompass all age groups, and consider adopting longitudinal or multicenter study designs, which will enhance the validity and applicability of results, and provide a more comprehensive understanding.

Given that this was a single-center study with a small patient population, larger-scale research is needed to provide findings that are more broadly applicable.

It is essential to stop these side effects and nutritional deficits while also extending patient life and improving patient quality. Children with beta thalassemia major in their second decade of life should take calcium and vitamin D supplements as a preventative step to help with bone development and avoid osteoporosis.

CONCLUSION

Almost a quarter of the patients presenting to a tertiary care hospital with Beta thalassemia major have osteoporosis. Hence, patients with adult thalassemia major should undergo screening for both vitamin D and bone mineral density (BMD) in order to diagnose bone damage early and start therapy early to prevent osteoporosis.

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