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Association of Bone Health in Children with Thalassemia: A Case-Control Study

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ABSTRACT

Background: Children with transfusion-dependent thalassemia (TDT) often experience a range of bone-related issues. This study was done to assess bone health in children with TDT by evaluating bone mineral density (BMD) and related biochemical markers.

Methods: This case-control study was conducted at the hematology department of the Children's Hospital and Institute of Child Health, Multan, from September 2024 to February 2025. Children aged 5–16 years with TDT, receiving regular transfusions and chelation for at least one year, were enrolled as cases, while age- and gender-matched healthy children served as controls. A total of 90 participants (45 per group) were recruited using non-probability consecutive sampling. Bone health was evaluated by dual-energy X-ray absorptiometry and relevant laboratory investigations. Data were analyzed in IBM-SPSS Statistics version 26.0, applying an independent sample t-test or chi-square test, with $p<0.05$ considered statistically significant.

Results: of 90 children, 46 (51.1%) were boys, while the mean age was 10.80±3.11 years. TDT children showed significantly lower lumbar spine Z-scores (-1.90±0.60 vs. -0.76±0.47, $p<0.001$) and femoral neck Z-scores (-1.83±0.56 vs. -0.81±0.40, $p<0.001$). Osteoporosis was present in 9 (20%) children, and 36 (80%) had osteopenia. TDT children had lower vitamin D (10.54±3.93 ng/ml vs. 20.93±7.54 ng/ml, $p<0.001$), calcium, and phosphorus levels, but higher alkaline phosphatase and parathyroid hormone levels ($p<0.001$).

Conclusion: Children with TDT have significantly lower BMD, with a high prevalence of osteopenia and osteoporosis. Vitamin D deficiency, lower serum calcium and phosphorus levels, and increased bone turnover were key contributors to poor bone health in TDT patients.

Keywords: Bone Mineral Density, Osteopenia, Osteoporosis, Thalassemia, Vitamin D.

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INTRODUCTION

Hemoglobinopathies such as thalassemia account for 3.4% mortality worldwide among children under the age of 5 years[1]. Global estimates indicate that 300000- 400000 children are born with inherited severe hemoglobin diseases every year, and approximately 80 million are β-thalassemia carriers[2,3]. Thalassemia is defined by chronic hemolytic anemia, necessitating regular blood transfusions to achieve sufficient hemoglobin levels. Thalassemia can be divided into various forms, including beta-thalassemia major, which is the most severe, and beta-thalassemia intermedia, a less severe form[4].

Children with transfusion-dependent thalassemia (TDT) often experience a range of bone-related issues, including osteopenia, osteoporosis, bone deformities, fractures, and growth retardation[5]. These complications may arise due to several factors, including chronic anemia, iron overload, and disturbances in calcium-phosphorus homeostasis[6]. Iron overload, which results from repeated transfusions, can accumulate in various organs, including bones, leading to impaired bone formation[7]. The chronic inflammatory state associated with thalassemia can negatively affect bone metabolism. Bone health is often overlooked, potentially leading to significant morbidity in thalassemia as these children grow older. A recent study from Iraq reported the proportion of osteoporosis among TDT and non-TDT to be 69.8% and 40.0%, respectively[8]. A study from Malaysia analyzing children and adolescents with TDT revealed that hypocalcemia, hypophosphatemia, and vitamin D deficiency (VDD) were observed in 22% and 18.2 %, and 85% respectively[9].

Despite raised risks, bone health is often neglected in thalassemia management[10]. This study sought to highlight the burden of bone-health related issues and biochemical markers. Exploring the association between bone health and TDT in children has been a topic of interest, but not much local work is available, so the present study was planned. This study may help in identifying bone mineral density (BMD) and biochemical markers of bone health in children with thalassemia. The objective was to assess bone health in children with TDT by evaluating BMD and related biochemical markers.

METHODS

This case-control study was conducted in the Hematology Department of "The Children's Hospital and Institute of Child Health, Multan", Pakistan from September 2024 to February 2025. Approval was obtained from the "Institutional Ethical Committee" (letter number: 1645, dated:28-08-2024). Written and informed consents were obtained from the parents or legal guardians. The sample size was calculated using the online OpenEpi sample size calculator. Taking the proportion of osteoporosis in children with and without TDT to be 69.8% and 40.0%, respectively8, with 95% confidence level, and 80% power, the sample size was calculated to be 90 (45 in each group). For cases, children of either gender, aged 5-16 years, with a confirmed diagnosis of TDT, receiving regular blood transfusions (at least 1 every 3-4 weeks), and chelation therapy for at least 1 year, were included. For controls, healthy children from the outpatient department among attendees, matched for age and gender, were included. Exclusion criteria were children with known metabolic bone disorders or chronic kidney disease, endocrine disorders, skeletal deformities, or those who had a history of any kind of orthopedic surgery. Children taking medications that could affect bone metabolism (e.g., corticosteroids, anticonvulsants) were also excluded. Non-probability, consecutive sampling technique was adopted.

Demographic data, along with detailed clinical history, were documented, and necessary laboratory investigations were performed. Bone status was measured using "dual-energy X-ray absorptiometry (DEXA)", and BMD was measured at the lumbar spine (L1-L4) and femoral neck (FN). Osteopenia and osteoporosis were labeled as Z-score between -1 and -2.5, and Z-score <-2.5, respectively. Moreover, 25-OH-D serum levels were utilized to determine vitamin D status, and ≥ 30 ng/ml or greater was deemed adequate. A special proforma was designed to record all study data. Data were analyzed using "IBM-SPSS Statistics, version 25.0". Descriptive statistics were used to represent data. Independent sample t-tests were used to compare continuous variables such as BMD, serum calcium, and vitamin D levels between the case and control groups. Chi-square tests were used for categorical variables such as the prevalence of osteopenia and osteoporosis. Pearson's correlation was examined to identify a relationship between BMD with other quantitative variables. $P<0.05$ was considered statistically significant.

RESULTS

Table 1: Comparison of Demographic Characteristics in Study Groups (N=90)

Characteristics		Transfusion-Dependent Thalassemia (n=45)	Controls (n=45)	P-value
Gender	Boys	22 (48.9%)	22 (48.9%)	1
	Girls	23 (51.1%)	23 (51.1%)	
Age (years)		10.87±3.06	10.73±3.19	0.840
Weight (kg)		28.87±6.24	31.94±6.39	0.023
Height (cm)		122.22±14.43	124.21±14.08	0.508
Duration of disease		4.73±2.72	-	-

Table 1 shows details about the comparison of the demographic characteristics of patient in both study groups. Out of 90 children, 46 (51.1%) were boys. The mean age, and duration of thalassemia were 10.80±3.11 years (ranging between 5 to 15 years), and 4.73±2.73 years, respectively. The mean age was statistically similar between groups (10.87±3.06 vs. 10.73±3.19 years, p=0.840). TDT children had significantly lower mean weight (28.87±6.24 vs. 31.94±6.39 kg, p=0.023), while height was comparable (p=0.508).

Table 2: Comparison of Bone Health-Related Findings in Both Study Groups (N=90)

Characteristics		Transfusion-Dependent Thalassemia (n=45)	Controls (n=45)	P-value
BMD Lumbar Spine (Z-Score)	Mean±SD	-1.90±0.60	-0.76±0.47	<0.001
	Osteoporosis	9 (20.0%)	-	<0.001
	Osteopenia	36 (80.0%)	17 (37.8%)	
	Normal	-	28 (62.2%)	
BMD Femoral Neck (Z-Score)	Mean±SD	-1.83±0.56	-0.81±0.40	<0.001
	Osteoporosis	7 (15.6%)	-	<0.001
	Osteopenia	38 (84.4%)	17 (37.8%)	
	Normal	-	28 (62.2%)	
Vitamin D (ng/ml)		10.54±3.93	20.93±7.54	<0.001
Vitamin D deficiency		45 (100%)	36 (80.0%)	0.002
Serum Calcium (mg/dl)		9.02±0.45	9.42±0.56	<0.001
Serum Phosphorus (mg/dl)		3.79±0.60	4.30±0.37	<0.001
Alkaline phosphatase (U/L)		251.15±57.56	175.70±45.21	<0.001
Parathyroid hormone (pg/ml)		42.74±14.28	28.79±11.56	<0.001

Table 2 shows BMD results showed significantly lower lumbar spine Z-scores in TDT children (-1.90 ± 0.60 vs. -0.76 ± 0.47, p<0.001), with 9 patients (20.0%) having osteoporosis and 36 (80.0%) having osteopenia. In comparison, 17 (37.8%) controls had osteopenia, while 28 (62.2%) had normal BMD. Similar trends were seen in FN Z-scores (-1.83±0.56 vs. -0.81±0.40, p<0.001), and 7 (15.6%) had osteoporosis and 38 (84.4%) with osteopenia. TDT children had significantly lower vitamin D levels (10.54 ± 3.93 ng/ml) compared to controls (20.93 ± 7.54 ng/ml, p<0.001). Serum calcium (9.02±0.45 mg/dL vs. 9.42±0.56 mg/dL, p<0.001) and phosphorus (3.79±0.60 mg/dL vs. 4.30±0.37 mg/dL, p<0.001) were lower in TDT children. ALP (251.15±57.56 U/L and 42.74±14.28 pg/mL, p<0.001), and parathyroid hormone levels (175.70±45.21 U/L and 28.79±11.56 pg/mL, p<0.001) were significantly higher in TDT children, as shown in table-2. A significant inverse correlation was found between thalassemia and BMD (r=-0.48, p<0.01). Vitamin D levels had having significant positive correlation with BMD (r=0.41, p<0.01).

DISCUSSION

This study confirms a strong association between TDT and impaired bone health in children, as evidenced by the higher prevalence of osteopenia and osteoporosis among children with TDT. In this study, 80% of children with TDT were found to have osteopenia, while 20% had osteoporosis, based on lumbar spine BMD Z-scores. In comparison, only 37.8% of controls showed osteopenia, and none had osteoporosis. These findings are consistent with another study, where 46% of TDT patients had spine BMD Z-scores<-2.011. A significant decline in BMD at FN and total body was also documented, with 11.6% of patients experiencing fractures, a complication often associated with osteoporosis[11]. This suggests that children with TDT are at substantial risk for poor bone health, with a high likelihood of progressing to osteoporosis if not managed appropriately. The present findings further underscore the susceptibility of TDT children to low bone mass. The mean lumbar spine Z-score in TDT children was 1.90±0.60, significantly lower than the -0.76±0.47 observed in

controls (p<0.001). Similarly, the FN Z-scores were significantly reduced in the TDT group (-1.83±0.56 vs. -0.81±0.40, p<0.001). These results are corroborated by others, who found that BMD at the FN declined at a rate of 0.02 Z-score per year, with a more pronounced decrease in males[11]. Chronic anemia, iron overload, and endocrine complications such as hypogonadism contribute to impaired bone metabolism, leading to reduced bone density[12]. A study reported that 46.8% of thalassemia major cases had impaired puberty, and this was significantly associated with lower BMD[13]. Serum osteoprotegerin levels are significantly lower in TDT children, indicating that the process of bone formation is impaired in these patients[14]. On the other hand, another study found that 36% of thalassemia patients had osteopenia, with no major differences concerning gender distribution[15]. This study also found no gender difference in BMD, suggesting that both genders having TDT were at relatively equal risk for poor bone health.

VDD was another important finding in this study, with mean serum levels of 10.54±3.93 ng/m. In the TDT group, compared to 20.93±7.54 ng/ml in controls (p<0.001). This marked deficiency in vitamin D levels could be explained by multiple attributes like limited sun exposure, inappropriate dietary intake, and administration of iron chelation therapy, which interferes with vitamin D metabolism[16]. A significant relationship between vitamin D and BMD suggested that VDD could have a vital underlying role in reducing bone density in TDT. Similar findings were reported from Iran, where it was noted that VDD was prevalent in 45.5% of thalassemia patients and was significantly associated with lower BMD[17]. Researchers in the past have emphasized the role of vitamin D in ensuring bone health[18,19]. Vitamin D aids in calcium absorption as well as bone mineralization, while its deficiency may raise the chances of osteopenia and osteoporosis[20]. Hemoglobin levels have been positively correlated with higher BMD in a previous study, suggesting that maintaining higher hemoglobin levels through regular transfusions may help mitigate bone loss in TDT patients[11].

The mean serum calcium in TDT children was 9.02±0.45 mg/dL, compared to 9.42±0.56 mg/dL in controls (p<0.001), while serum phosphorus was 3.79±0.60 mg/dL in TDT patients versus 4.30±0.37 mg/dL in controls (p<0.001). Similar reductions in calcium, and phosphorus levels were reported in TDT patients in another study[21]. Lower calcium levels in thalassemia patients may be due to poor dietary intake, VDD, and iron overload, which disrupts calcium metabolism[22] Hypoparathyroidism, a common complication in thalassemia patients, may also contribute to decreased calcium levels[23]. Hypoparathyroidism was present in 7.8% of thalassemia patients and was significantly associated with lower BMD in another study[13]. Hypoparathyroidism results in reduced secretion of PTH, which is responsible for regulating calcium and phosphorus levels in the blood[24]. In this study, PTH levels were significantly elevated in TDT patients (42.74±14.28 pg/mL) compared to controls (28.79±11.56 pg/mL, p<0.001). Raised PTH levels may be leading to relatively higher bone resorption, further exacerbating the bone loss[25].

This study underscores the importance of integrating DEXA scans into regular follow-up protocols. The observed deficiencies in vitamin D, calcium, and phosphorus, along with elevated bone turnover markers, indicate a need for proactive nutritional supplementation and endocrine evaluation. Early identification and management of these abnormalities can help reduce fracture risk, improve quality of life, and prevent long-term skeletal complications in this vulnerable pediatric population. This study had several limitations. While assessment of serum vitamin D, calcium, phosphorus, and PTH levels were done, other factors such as ferritin and liver function tests were not measured. This study did not evaluate fracture incidence or bone pain, both of which are important clinical outcomes related to low BMD.

CONCLUSION

This study demonstrated that children with TDT have significantly lower BMD, with a high prevalence of osteopenia, and osteoporosis. VDD, lower serum calcium and phosphorus levels, and increased bone turnover were key contributors to poor bone health in TDT patients.

LIST OF ABBREVIATIONS

ALP: Alkaline phosphatase
BMD: Bone mineral density
DEXA: Dual-energy X-ray absorptiometry
FN: Femoral neck
PTH: Parathyroid hormone
SPSS: Statistical Package for Social Sciences
TDT: Transfusion-dependent thalassemia
VDD: Vitamin D deficiency

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CONFLICT OF INTEREST

The authors have no conflict of interest.

ETHICAL APPROVAL

The ethical approval for the Institutional Ethical Committee through letter ERC#: 1645,

dated:28-08-2024.

AUTHORS' CONTRIBUTION

MT: Conception, design, data collection, proofreading, critical revisions, approved for publication **ZA**: Drafting, data collection, proofreading, critical revisions, approved for publication **MI**: Conceived the idea, drafted, data analysis, proofreading, critical revisions, approved for publication **GAQ**: Literature review, data analysis, proofreading, critical revisions, approved for publication.

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