Section: Pediatrics

Original Research Article

CROSS-SECTIONAL STUDY OF BONE MINERAL PROFILE IN TRANSFUSION-DEPENDENT THALASSEMIA CHILDREN

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Abstract

Background: Thalassemia is a hereditary blood disorder characterized by reduced haemoglobin synthesis that leads to severe anaemia and various systemic complications. This study investigated bone mineral profiles and associated biochemical parameters in children with transfusion-dependent thalassemia. **Materials and Methods:** A cross-sectional study was conducted involving 34 children with transfusion-dependent thalassemia admitted to the Institute of Child Health & Hospital for Children, Chennai, between December 2019 and August 2020. The inclusion criteria encompassed children with a minimum of 20 transfusions, while those with comorbid conditions affecting bone metabolism were excluded. Clinical histories were collected, followed by comprehensive examinations and laboratory investigations including serum calcium, phosphorus, alkaline phosphatase, ferritin, and vitamin D levels. BMD was assessed using bone mineral densitometry. **Result:** The mean age of the participants was 8.21 ± 3.39 years. Notable findings included no significant differences in serum calcium, phosphorus, vitamin D, or alkaline phosphatase levels between anaemic and non-anaemic children ($p > 0.05$). However, significant correlations were observed: serum ferritin levels were negatively correlated with serum calcium ($r = -0.36$, $p = 0.05$) and BMD T-score ($r = -0.26$, $p = 0.03$) and positively correlated with serum phosphorus ($r = 0.39$, $p = 0.02$). Vitamin D levels also showed a significant negative correlation with serum ferritin levels ($p < 0.05$). **Conclusion:** This study highlights the complex interplay between thalassemia management and bone health, emphasizing the need for routine monitoring of bone mineral density and biochemical parameters in children with transfusion-dependent thalassemia to prevent complications such as osteopenia and osteoporosis.

INTRODUCTION

Thalassemia is a serious global health issue, particularly in areas with high carrier rates, such as Southeast Asia and Africa. This hereditary disorder, caused by a defect in the globin gene, reduces the synthesis of haemoglobin and comes in various clinical forms, mainly β-thalassemia.[1] The term "thalassemia" is derived from the Greek words "thalassa" or sea and "haima" or blood, showing its origin from the Mediterranean area.[2] It is explained by more than 200 identified mutations and has various clinical presentations that range from asymptomatic carriers to severe forms requiring chronic blood transfusions.[3]

In children with thalassemia major, there will be an enormous deficiency or lack of synthesis of the beta-globin chain, which produces severe anaemia in most of the cases and typically begins when they are six months old.[3,4] The manifestations will primarily comprise growth retardation, jaundice, pallor, and skeletal abnormalities through extramedullary hematopoiesis and bone marrow overstimulation.[5] In such patients, life-long interventions for complications resulting from iron overload would have been administered through blood transfusions and iron chelation therapy.

Thalassemia intermedia appears with less severe conditions and inconsistent degrees of anaemia that do not necessitate chronic transfusions.[6] β-thalassemia is accompanied by mild anaemia and increased levels of HbA2 and fetal haemoglobin. The manifestations of thalassemia are no longer limited to its haematologic features but encompass many

systemic complications due to repetitive transfusions, making the patient more prone to infections, among significant psychosocial challenges.[4,6]

For example, complications from chronic blood transfusions are a common problem for patients with thalassemia, primarily iron overload.[7] Some organs, including the heart, liver, and endocrine glands, start to deteriorate. In addition to that, it has a great effect on bone health; thalassemic children often face skeletal complications, such as osteopenia and osteoporosis, due to disturbances in the metabolism of bone minerals.[8] These abnormalities result from factors such as impaired osteoblast activity, increased osteoclast activity, and hormonal deficiencies.

Thalassemia-induced changes in bone turnover are characterized by higher rates of resorption while at the same time having lower bone tissue formation rates.[9] This disparity results in lower mineral bone density and increased risks of fractures and deformities. Studies show that therapeutic targets for thalassemia-induced osteoporosis exist regarding the Wnt signaling pathway.[10]

The cross-sectional study designed to investigate the bone mineral profile in transfusion-dependent thalassemia children aimed at broadly understanding the interplay of thalassemia management with bone health. Its contribution intends to shed valuable light on improving the outcomes for affected children while addressing the broader implications of this chronic condition on their quality of life.

AIM

This study aimed to evaluate the bone-related biochemical profile, assess bone mineral density through bone densitometry scans, and identify early-onset osteopenia in children with transfusion-dependent thalassemia.

MATERIALS AND METHODS

This cross-sectional study was carried out among 34 children with transfusion-dependent thalassemia admitted to the haematology ward in the Institute of Child Health & Hospital for Children, Chennai, from December 2019 to August 2020.

Inclusion criteria:

Children suffering from thalassemia who had received at least 20 transfusions.

Exclusion criteria:

Thalassemic children with any other comorbid conditions predisposing them to bone mineral derangements, such as renal tubular acidosis and chronic kidney disease, were excluded from the study.

Informed consent was taken from the parents of the children ensuring confidentiality. Thereafter, there was collection of extensive clinical history of them that included such basic epidemiological details, mode of diagnosis, and previous treatment history and transfusion history.

A general examination was conducted along with a systemic examination of the cardiovascular system (CVS), respiratory system (RS), central nervous system (CNS), and abdomen. The necessary investigations included a complete hemogram, serum calcium (total and ionized), serum phosphorus, serum alkaline phosphatase, total proteins (including serum albumin and globulin), serum ferritin, vitamin D levels, and bone mineral densitometry scan.

Statistical analysis: Using a pretested pro forma, detailed patient history, clinical findings, investigations, and treatment were documented. All the data were statistically analysed, and Krukal Wallis, chi-square test were used. Correlations between the clinical variables were calculated using the Spearman Rank correlation method.

RESULTS

The mean age was 8.21 ± 3.39 years. The male average age was 8.89 ±3.86 years and the female average age was 7.33 ± 2.55 years, which is not significant.

There were no significant differences in calcium, phosphorus, vitamin D, and Alk phosphate levels between anaemic and non-anaemic children ($p>0.05$) [Table 1].

There was no significant difference in age group, gender, haemoglobin, and Sr Alk.PO4ase between Sr Ferritin ($p>0.05$). We found that the Sr Ferritin levels of Vitamin D sufficient children, Vitamin D insufficient children, and Vitamin D Deficient children were 2132.33 ng/ml, 2556.21 ng/ml, and 4280.83 ng/ml with a significance respectively.

The association between Sr Calcium and Sr Ferritin showed that normal children have 2041.60 Sr ferritin and low-level calcium children have 3802.65 Sr ferritin, with a significant difference. The association between Sr Phosphorus and Sr ferritin indicated that normal children have 2610.34 Sr Ferritin, and high-level Sr Phosphorus children have 4092.78 Sr Ferritin, which is a significant difference [Table 3].

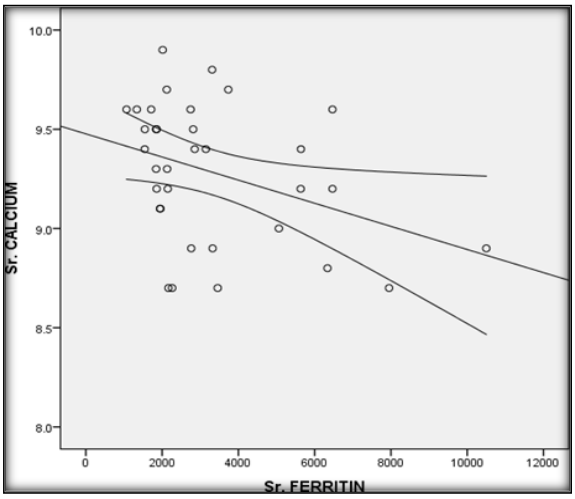

Figure 1: A scatter diagram with regression estimates shows a negative (r=-0.36, p≤0.05) correlation coefficient between children's serum ferritin and serum calcium scores.

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We found a significant negative correlation between serum ferritin and calcium levels. In other words, serum ferritin levels increased, and serum calcium levels decreased. On the other hand, there was a significant positive correlation between serum ferritin levels and serum phosphorus levels. This means that serum ferritin and phosphorus levels increase.

The correlation between serum ferritin and vitamin D showed that there is a significant, negative correlation between serum ferritin and vitamin D. In other words, as serum ferritin levels increase, vitamin D levels decrease. Similarly, there was a significant negative correlation between children's serum ferritin levels and BMD T-scores. This means that serum ferritin increases the BMD T-score and also decreases it [Table 4].

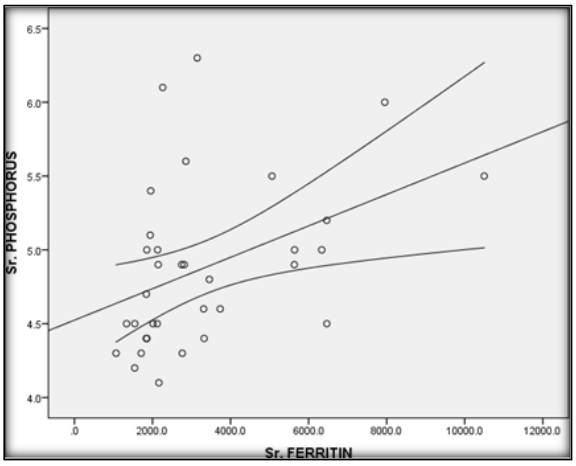

Figure 2: A scatter diagram with regression estimates shows a positive (r=0.39, p≤0.02) correlation coefficient between children's serum ferritin and serum phosphorus scores.

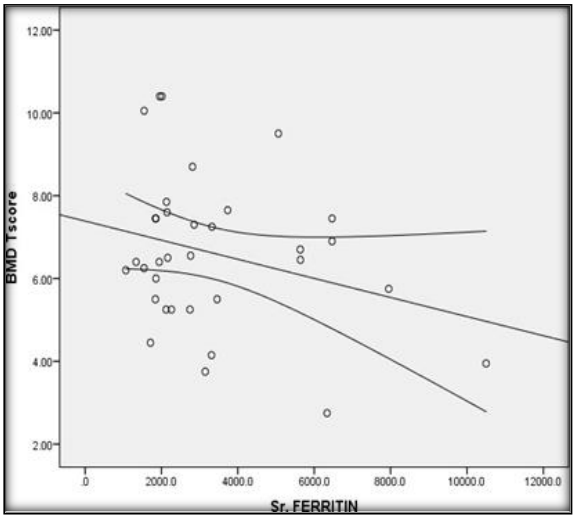

Figure 3: A scatter diagram with regression estimates shows a positive (r=0.39, p≤0.02) correlation coefficient between children's serum ferritin and BMD T-score.

We found a significant negative fair correlation between serum ferritin levels in children and their BMD T-scores. This means that the BMD T-score decreased, and serum ferritin levels increased fairly. A significant positive correlation was observed between the children's BMD T-scores and their serum calcium levels. This means that BMD T-scores increase, and their serum calcium levels also increase. Likewise, there was a significant positive correlation between children's BMD T-scores and Vitamin D levels. This means that the BMD T-score increased and their Vitamin D levels increased fairly [Table 5].

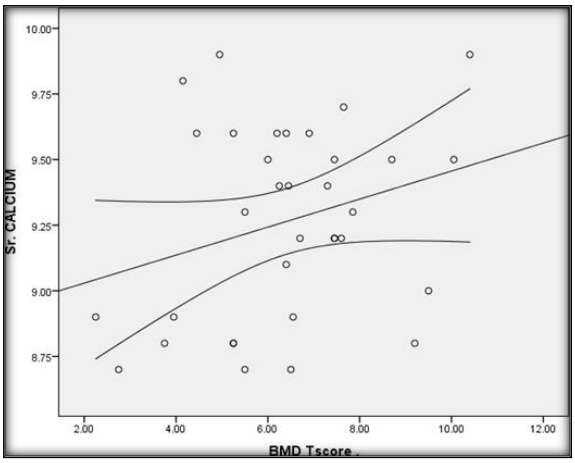

Figure 4: A scatter diagram with regression estimates shows a positive (r=0.38, p≤0.02) correlation coefficient between children's BMD T-score and serum calcium.

We found a significant positive correlation between chelation dose and serum ferritin level. This means that chelation doses increase and serum ferritin levels increase. There was a significant negative correlation between the chelation dose and vitamin D level. This means that the chelation doses increased, and vitamin D levels decreased.

There was a significant negative correlation between pre-transfusion haemoglobin and serum ferritin levels. This means that pre-transfusion haemoglobin decreases and serum ferritin levels increase. However, a significant positive correlation was observed between pre-transfusion haemoglobin and vitamin D levels. This means that pre-transfusion haemoglobin levels decreased and vitamin D levels decreased fairly. Similarly, there was a positive correlation between pre-transfusion haemoglobin and age. This means that pre-transfusion haemoglobin levels increase as age increases [Table 6].

There was a significant association between the levels of vitamin D (ng/ml), Sr Calcium (mg/dl) and Sr phosphorus (mg/dl) in children with thalassemia. The association between calcium and vitamin D was studied, and we found that four normal children had sufficient vitamin D (14.81%), 12 had insufficient vitamin D (44.44%), and 11 had deficient vitamin D (40.74%), whereas 7 children with hypocalcaemia had deficient vitamin D levels (100%).

On the other hand, the association between Sr Phosphorus and vitamin D showed that four children with normal phosphorus had (14.28%) sufficient vitamin D, 12 (42.86%) had insufficient vitamin D,

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and 12 (42.86%) had deficient vitamin D levels, whereas six children with high Sr phosphorus (100%) had deficient vitamin D levels [Table 7].

There was a significant association between the levels of VITAMIN D (ng/ml), calcium (mg/dl), and phosphorus (mg/dl) in children with thalassemia. Children with normal and low calcium levels had vitamin D levels, found to be 22.28 and 15.81, respectively, with significant differences.

The association between vitamin D and Sr phosphorus showed that children with normal Sr Phosphorus and high Sr phosphorus levels had vitamin D levels, found to be 21.84 and 14.75, respectively [Table 8].

We found a significant negative correlation between vitamin D and serum ferritin, indicating that vitamin D decreases as serum ferritin increases. We found a significant positive correlation between children's vitamin D and serum calcium levels. This means that both vitamin D and serum calcium levels increase.

There was a significant negative correlation between vitamin D levels and serum phosphorus levels. In other words, as vitamin D levels decreased, serum phosphorus levels increased. However, there was a significant positive correlation between vitamin D and BMD T-score. In other words, as vitamin D levels decreased, their BMD T-scores also decreased [Table 9].

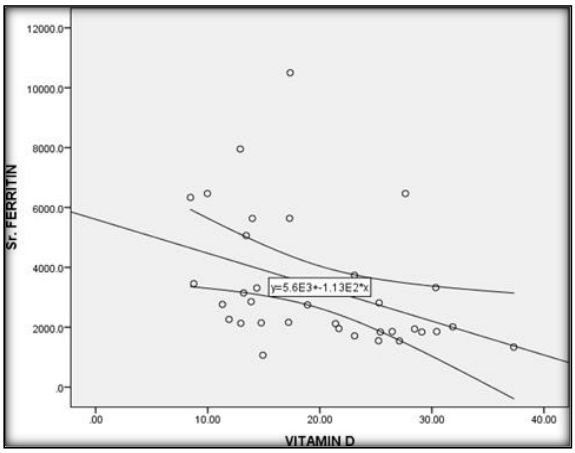

Figure 5: The scatter diagram with regression estimate shows a fairly negative (r=-0.38, p≤0.05) correlation coefficient between Vitamin D and Serum Ferritin scores.

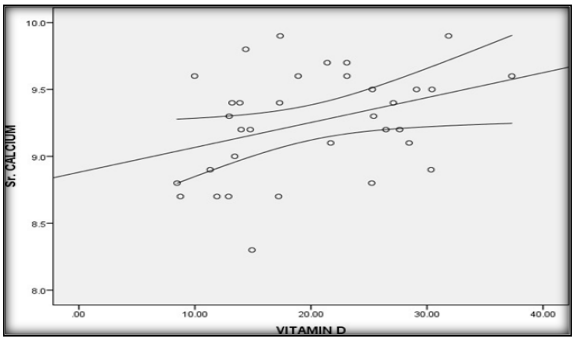

Figure 6: A scatter diagram with regression estimates shows a positive (r=0.36, p≤0.05) correlation coefficient between Vitamin D and Serum Calcium score.

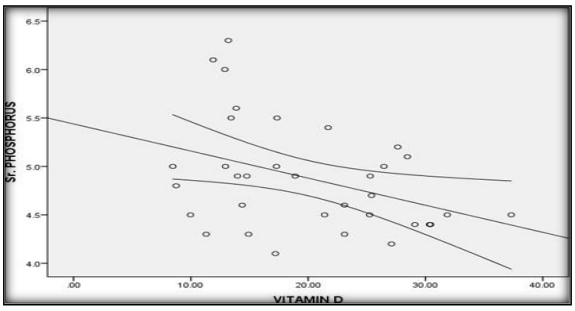

Figure 7: A scatter diagram with regression estimates shows a negative (r=-0.39, p≤0.05) correlation coefficient between vitamin D and Serum phosphorus score.

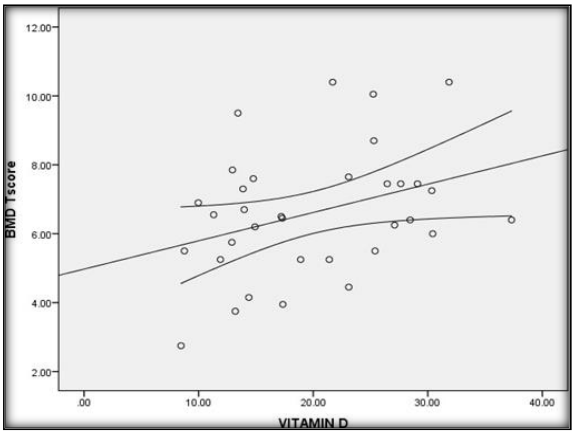

Figure 8: The scatter diagram with regression estimate shows the fair positive (r=0.35, p≤0.05) correlation coefficient between vitamin D and BMD T score.

Table 1: Comparison of calcium, phosphorus, vitamin D, and Alk phosphate between children.

		N (%)	Anaemic children (<10) (n=21)	Non anaemic children (>10) (n=13)	P value
Level of calcium	Normal (8.8 -11)	27 (79.41%)	19	12	0.85, □2=0.03
	Low (<8.8)	7 (20.59%)	2	1	
	High (>11)	0	0	0	
Level of phosphorus	Normal (3.2-5.5)	28 (82.35%)	19	10	0.23, □2=1.17
	Low (<3.2)	0	0	0	
	High (>5.5)	6 (17.65%)	2	3	
Level of vitamin D	Sufficient (30-100)	4 (11.76%)	2	3	0.44, □2=1.62
	Insufficient (20-30	12 (35.29%)	7	5	
	Deficient (<20)	18 (52.94%)	12	5	
Level of Sr. Alk. PO4ase	Normal (60-320)	32 (94.12%)	19	13	0.15, □2=2.08
	Low (<60)	0	0	0	
	High (>320)	2 (5.88%)	2	0	

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Table 2: Demographic and clinical variables

	Mean SD
Age (years)	8.21 ± 3.39
Haemoglobin (g/dl)	8.88 ± 2.09
Haematocrit	26.05 ± 6.22
Sr. Calcium (mg/dl)	9.33 ± 0.42
Sr. Phosphorus (mg/dl)	5.01 ± 0.58
Vitamin D (ng/ml)	19.98 ± 7.67
Sr. Alk.PO4ase	189.82 ± 75.67
Sr. Total Proteins (g/dl)	7.27 ± 0.62
Sr. Albumin (g/dl)	4.36 ± 0.29
Sr. Globulin (g/dl)	2.91 ± 0.66
Sr. Ferritin (ng/ml)	3419.37 ± 2847.51
BMD T score	6.41 ± 1.92

Table 3: Association between Sr Ferritin (ng/ml) and clinical variables

		Sr. Ferritin (ng/ml)	P value
Age group (years)	< 5	2668.74 ± 1646.43	□2=4.37, p=0.11
	6 -10	2682.61 ± 1228.48	
	11-15	5478.28 ± 4644.41	
Gender	Male	3903.14 ± 3563.39	t=0.53, p=0.60
	Female	2806.61 ± 1437.63	
Haemoglobin (g/dl)	Normal	2976.97 ± 2011.69	t=0.86, p=0.38
	Anaemic	3693.24 ± 3277.89	
Sr. Calcium (mg/dl)	Normal	2041.6 ± 2394.27	z=2.01, p=0.05
	Low	3802.65 ± 1619.47	
	High	0	
Sr. Phosphorus (mg/dl)	Normal	2610.34 ± 1947.67	□2=2.07, p=0.05
	Low	0	
	High	4092.78 ± 2448.89	
Vitamin D	Sufficient	2132.33 ± 845.19	□2=6.25, p=0.04
	Insufficient	2556.21 ± 1408.16	
	Deficient	4280.83 ± 3553.74	
Sr. Alk.PO4ase	Normal	3448.93 ± 2934.88	□2=0.13, p=0.71
	Low	0	
	High	2946.45 ± 282.49	

Table 4: Correlation between children's serum ferritin score and their clinical variables

Correlation between	Sr. Ferritin (3419.37 ± 2847.51) vs	Spearman Rank Correlation coefficients	Interpretation
Sr. Calcium	9.33 ± 0.42	r= -0.36, P=0.05*	Negative correlation
Sr. Phosphorus	5.01 ± 0.58	r= 0.39, P=0.02*	Positive correlation
Sr. Alk.po4ase	189.82 ± 75.67	r= 0.11, P=0.41	Positive correlation
Total proteins	7.27 ± 0.62	r= 0.15, P=0.26	Positive correlation
Sr. Albumin	4.36 ± 0.29	r= 0.09, P=0.31	Positive correlation
Sr. Globulin	2.91 ± 0.66	r= 0.12, P=0.14	Positive correlation
Vitamin D	19.98 ± 7.67	r= -0.38, P=0.02*	Negative correlation
BMD T score	6.41 ± 1.92	r= -0.26, P=0.03*	Negative correlation

Table 5: Correlation between BMD T-score and their clinical variables

Correlation between	BMD T score (6.41 ± 1.92) vs	Spearman Rank Correlation coefficients	Interpretation
Sr. Calcium	9.33 ± 0.42	r= 0.38, P=0.03*	Positive correlation
Sr. Phosphorus	5.01 ± 0.58	r= -0.24, P=0.15	Negative correlation
Sr. Alk.po4ase	189.82 ± 75.67	r= -0.11, P=0.54	Negative correlation
Total proteins	7.27 ± 0.62	r= -0.21, P=0.23	Negative correlation
Sr. Albumin	4.36 ± 0.29	r= 0.13, P=0.61	Negative correlation
Sr. Globulin	2.91 ± 0.66	r= 0.17, P=0.27	Negative correlation
Vitamin D	19.98 ± 7.67	r= 0.35, P=0.02*	Positive correlation
Sr. Ferritin score	3419.37 ± 2847.51	r= -0.26, P=0.03*	Negative correlation

Table 6: Correlation between chelation doses, pre-transfusion haemoglobin and their clinical variables

	Chelation doses (56.82±34.04) vs	Spearman Rank Correlation coefficients	Interpretation
Sr. Ferritin	3419.37±2847.51	r= 0.28 P=0.11	Positive correlation
Vitamin D	19.98±7.67	r= -0.10 P=0.55	Negative correlation
	Pre-transfusion haemoglobin (9.08±2.68)	Spearman Rank Correlation coefficients	Interpretation
Sr. Ferritin	3419.37±2847.51	r= -0.18 P=0.29	Negative correlation
Vitamin D	19.98±7.67	r= 0.14 P=0.42	Positive correlation
Age	8.21 ± 3.39	r= 0.10 P=0.59	Positive correlation

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Table 7: Association between level of vitamin D and clinical variables

		Level of Vitamin D			P value
		Sufficient	Insufficient	Deficient	
Age group (years)	< 5	2 (25%)	3 (37.5%)	3 (37.5%)	c2=4.38, p=0.36
	6 -10	2 (11.76%)	7 (41.18%)	8 (47.06%)	
	11-15	0	2 (22.22%)	7 (77.78%)	
Haemoglobin (g/dl)	Normal	2 (15.38%)	5 (38.46%)	6 (46.15%)	c2=0.48, p=0.79
	Anaemic	2 (9.52%)	7 (33.33%)	12 (57.14%)	
Sr. Calcium (mg/dl)	Normal	4 (14.81%)	12 (44.44%)	11 (40.74%)	c2=7.83, p=0.02
	Low	0	0	7	
	High	0	0	0	
Sr. Phosphorus (mg/dl)	Normal	4 (14.28%)	12 (42.86%)	12 (42.86%)	c2=6.48, p=0.04
	Low	0	0	0	
	High	0	0	6 (100)	
Sr. Alk.PO4ase	Normal	4 (12.5%)	12 (37.5%)	16 (50%)	c2=1.88, p=0.38
	Low	0	0	0	
	High	0	0	2	

Table 8: Association between vitamin D (NG/ML) and clinical variables

		N	Vitamin D (ng/ml)	P value
Age group (years)	< 5	8	22.1 ± 9.65	c2=3.75 p=0.15 (NS)
	6 -10	17	20.79 ± 7.52	
	11-15	9	16.58 ± 5.41	
Gender	Male	19	21.01 ± 6.78	Z=0.85 p=0.40 (NS)
	Female	15	18.69 ± 8.74	
Haemoglobin (g/dl)	Normal	13	21.56 ± 7.58	Z=0.45 p=0.50 (NS)
	Anaemic	21	19.01 ± 7.75	
Sr. Calcium (mg/dl)	Normal	27	22.28 ± 7.6	z=2.10 p=0.04 (S)
	Low	7	15.81 ± 9.09	
	High	0	0	
Sr. Phosphorus (mg/dl)	Normal	28	21.84 ± 7.54	c2=2.01 p=0.05 (S)
	Low	0	0	
	High	6	14.75 ± 8.48	
Sr. Alk.PO4ase	Normal	2	20.23 ± 7.82	c2=1.30 p=0.19 (NS)
	Low	13	0	
	High	21	16.05 ± 4.03	

Table 9: Correlation between vitamin D score and their clinical variables

Correlation between	Vitamin D (19.98±7.67)	Spearman Rank Correlation coefficients	Interpretation
Sr. Calcium	9.33±0.42	r= 0.36, P=0.03	Positive correlation
Sr. Phosphorus	5.01±0.58	r=- 0.39, P=0.02	Negative correlation
Sr. Ferritin	3419.37±2847.51	r= -0.38, P=0.02	Negative correlation
BMD T score	6.41±1.92	r= 0.35, P=0.02	Positive correlation

DISCUSSION

In this study, of 34 children who had more than 20 transfusions since diagnosis, preliminary details were recorded, a history of diagnosis of thalassemia was asked for, and history related to transfusion, chelation therapy, complete hemogram, bone-related biochemical profile (calcium, phosphorus, alkaline phosphatase, vitamin D, ferritin, and bone mineral densitometry) were performed.

Borkar et al. study evaluated BMD in transfusion-dependent thalassemic children and concluded that a significant correlation existed between BMD and Sr ferritin and vitamin D levels.[11] In our study, there was a negative correlation between BMD and serum ferritin levels, and a positive correlation between BMD and vitamin D levels, following the above study.

Sultan et al. study evaluated the biochemical markers of bone turnover, found hypocalcemia 66.6%, hypophosphatemia 19.4%, vitamin D deficiency 72.2%, and found a significant direct correlation between Sr phosphorus and Sr ferritin levels.[12] In our study, hypocalcemia is seen in 20.59%, hyperphosphatemia is seen in 17.65%, 52.94% had deficient vitamin D levels and 35.29% had insufficient vitamin D levels.

Aparna et al. reported vitamin D deficiency was noted in 80-90%; however, in our study, it was 52.94%. Social and environmental factors could be responsible for these changes in vitamin D levels compared with previous studies.[13,14]

El Edel et al. evaluated BMD and vitamin D receptor polymorphism and found that vitamin D was significantly reduced in the BB vitamin D receptor genotype.[15] In our study, vitamin D levels were abnormally low in 87% of children with thalassemia. However, vitamin D receptor polymorphisms have not been taken into consideration.

Arslan et al. evaluated bone mineral density and biochemical markers and found that BMD was significantly lower in children with thalassemia.16 In our study, a significant association was observed between BMD and serum ferritin and vitamin D levels. We found a negative correlation between BMD and serum ferritin levels.

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CONCLUSION

In conclusion, children with transfusion-dependent thalassemia should be transfused appropriately at the right time to prevent bone marrow expansion and initiate chelation therapy. Children with thalassemia are more prone to vitamin D deficiency, which may lead to early-onset osteopenia. This could be prevented by providing vitamin D, calcium, and nutritional supplementation and performing bone mineral densitometry annually.

Limitations and recommendation: Vitamin D receptor polymorphism has not been studied, and iron overload by imaging could have been performed to look for iron deposits in the liver and other organs. This study recommends providing vitamin D and calcium supplementation to all transfusion-dependent thalassemia children when serum ferritin reaches 2500 ng/ml and conducts annual bone mineral density assessments using bone mineral densitometry.

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