ISSN (Print): 2663-9491 ISSN (Online): 2789-6897

Original Article

Impact of Calcium and Vitamin D Supplementation on Bone Mineral Content in Children Diagnosed with Thalassemia

DOI: dx.doi.org

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Received: 03 September 2023
Accepted: 21 September 2023
Published: 28 November 2023

Published by:
Sheikh Sayera Khatun Medical College (SSKMC), Gopalganj, Bangladesh

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ABSTRACT

Introduction: *This study aimed to assess the effect of vitamin D and calcium supplementation on osteoprotection in children with thalassemia.* ***Methods and Materials:*** *Twenty-nine children aged 5-18 years were administered oral vitamin D (600 IU/day) and calcium (500 mg/day) for a duration of one year. Dual-energy X-ray absorptiometry (DXA) was used to measure bone mineral content at the beginning of the study and after 12 months. Additionally, serum 25-hydroxy vitamin D, Serum parathyroid hormone, calcium and phosphate levels were assessed at baseline, 6 months, and 12 months.* ***Results:*** *The mean (SD) bone mineral content increased significantly from the baseline value of 9.3 g to 11.7 g. Similarly, the mean (SD) vitamin D level increased from the initial value of 17.0 ng/mL to 24.7 ng/mL.* ***Conclusions:*** *Supplementing with oral vitamin D and calcium enhances bone mineral content in children diagnosed with thalassemia over a period of one year.*

Keywords: *Thalassemia, Osteoporosis, Bone density, Cholecalciferol, Absorptiometry.*

(The Insight 2023; 6(1): 233-242)

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INTRODUCTION

Thalassemia, a common inherited disorder, affects millions of individuals worldwide, particularly in Southeast Asia, the Indian subcontinent, Mediterranean, Middle Asia, Central Asia, and West Africa. Globally, approximately 100 million individuals are estimated to have beta thalassemia, including approximately 100,000 children [1-3]. In Bangladesh alone, it is estimated that over 7,000 children are born with thalassemia each year [4-7]. Despite optimal management, children with transfusion-dependent thalassemia often have poor bone health, with osteoporosis affecting 40-80% of well-treated patients [8-10]. This is caused by various factors, including marrow expansion, chronic hypoxia, iron toxicity, use of iron chelators, endocrinopathies, nutritional deficiencies and vitamin D deficiencies [11-13]. The role of vitamin D and calcium supplementation in preventing osteoporosis in thalassemia requires further exploration [9, 12, 14].

METHODS AND MATERIALS

This study was conducted at the tertiary heath care center from March 2021 to September 2022 (1 year 6 months). This study was approved by the Institutional Review Board (IRB). This study aimed to assess the effect of *vitamin D* and *calcium* supplementation on *osteoprotection* in children with transfusion dependent thalassemia.

Thirty children aged 5-18 years were administered *oral vitamin D (600 IU/day)* and *calcium (500 mg/day)* for a duration of one year. A *dual energy X-ray absorptiometry (DXA)* scanner (*Hologic Company, USA*) was used to measure the bone mineral content at the beginning of the study and after 12 months. The instrument was meticulously calibrated with a measurement precision of within 1%. Children with hypocalcemic seizures, tetany, rickets, renal stones, chronic kidney disease, chronic liver disease, and those using phenytoin, immunosuppressants, or furosemide were excluded from the study.

Throughout the study, various parameters, including serum *25-hydroxy vitamin D (25(OH)D), parathyroid hormone (PTH),* calcium and phosphate were assessed at baseline, 6 months, and 12 months. Serum *25(OH)D* and *PTH* were assessed using the *chemiluminescence* method (*ADVIA Centaur*).

Children with baseline serum *25(OH)D* levels < 20 *ng/mL* received *oral vitamin D* at *1000 IU/day* for the first 2 months and then at *600 IU/day* for the remaining 10 months of the study. Patients with baseline *25(OH)D* levels above *20 ng/mL* were administered *vitamin D* at *600 IU/day* for 12 months. All the children in the study group received *500 mg* of calcium carbonate daily for the entire 12 months duration. Additionally, the enrolled children were monitored each month and received standard thalassemia care, including blood transfusions, chelation therapy, and growth monitoring. For children aged 5-18 years, the height-for-age *Z-score (HAZ)* for BMC was calculated according to *World Health Organization (WHO)* standards. Statistical analysis involved expressing data as mean and standard deviation, utilizing paired Student's *t-tests* to compare outcome variables before and after the intervention, and employing *Chi-square* tests to compare proportions. Data analysis was performed using *IBM® SPSS® Statistics version 29*

(*SPSS, Inc., Chicago*), with a significance level set at $P < 0.05$.

RESULTS

Fifty children diagnosed with thalassemia were evaluated for eligibility and enrolled in the study using consecutive sampling. Unfortunately, twenty-one children were lost to follow-up and were excluded from the analysis. The remaining 29 patients (16 boys and 13 girls) were meticulously monitored every month for one year. Of these patients, 27% did not receive iron chelation therapy, 49% were on *deferasirox* monotherapy, and 24% received a combination of *deferasirox* and *deferiprone*. Among the groups, 23% had serum ferritin levels < 100*ng/mL* and 77% had ferritin levels > 1600 *ng/mL*.

Alterations in bone health parameters and anthropometry are presented in ***Table I.***

Table I: Change in Bone Health Parameter.

Parameter	Baseline (n=29) Mean (SD)	After one year (n=29) Mean (SD)	P-value
Low weight for age (Z ≤-2), *n*(%)	16 (55%)	13 (45%)	0.517
Low height for age (Z ≤-2), *n*(%)	14 (48%)	15 (52%)	0.731
BMC (g)	9.37	11.82	<0.001
BMD (g/cm^2)	0.56	0.47	<0.001
***Low BMC (Z ≤-2)**	22	11	0.025
Vitamin D insufficiency (20-30ng/mL), *n*(%)	9 (31%)	0 (0%)	<0.001
Vitamin D deficiency (<20ng/mL)	12 (41.4)	6 (20.7)	<0.001
Serum 25-OH vitamin D (ng/mL)	13.84	14.92	<0.001
Serum Phosphate (mg/dL)	4.31	5.24	<0.001
Serum PTH (pg/mL)	37.90	42.03	<0.001
Serum Calcium (mg/dL)	8.92	9.63	<0.001

*BMC, bone mineral content; BMD, bone mineral density; DPD, deoxypyridinoline; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase; *Adjusted for height.*

Factors such as age, sex, anthropometric measurements, disease duration, previous transfusion history, serum ferritin levels, calcium profiles, *PTH* levels, *25-OH* Vitamin D levels, and bone turnover markers were not significantly associated with bone health status.

Figure I Presents a visual representation of the progression of weight and height of the studied children, both at baseline and after one year.

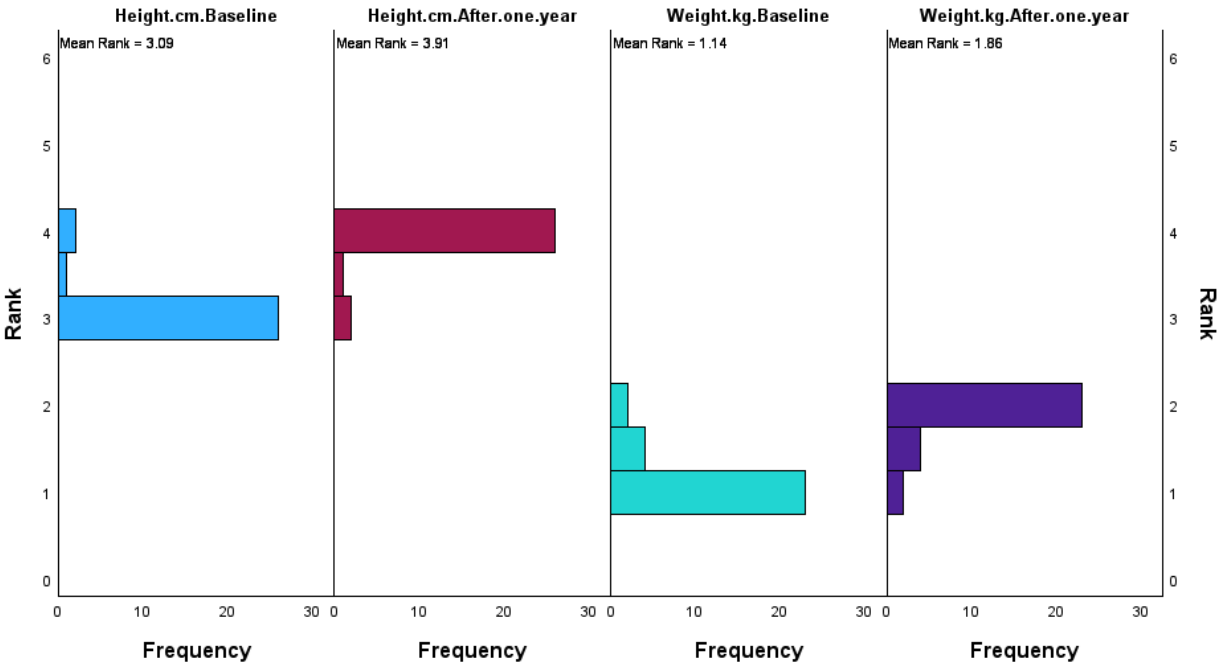

Figure I: Baseline and after one year height and weight of the studied children.

Figure II illustrate that supplementation significantly increases bone mineral content (BMC) among boys and girls over the period of one year in this populatio

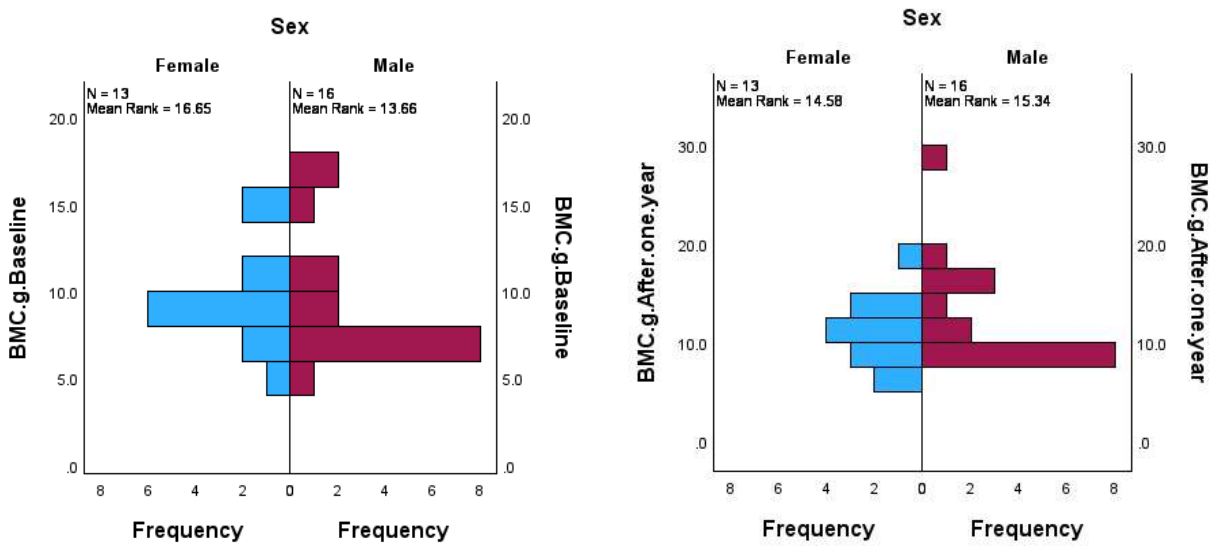

Figure II: Baseline and after one year bone mineral content (BMC) according to sex.

Figure III illustrates the significant increase in bone mineral density (BMD) among boys and girls over the one-year period resulting from supplementation.

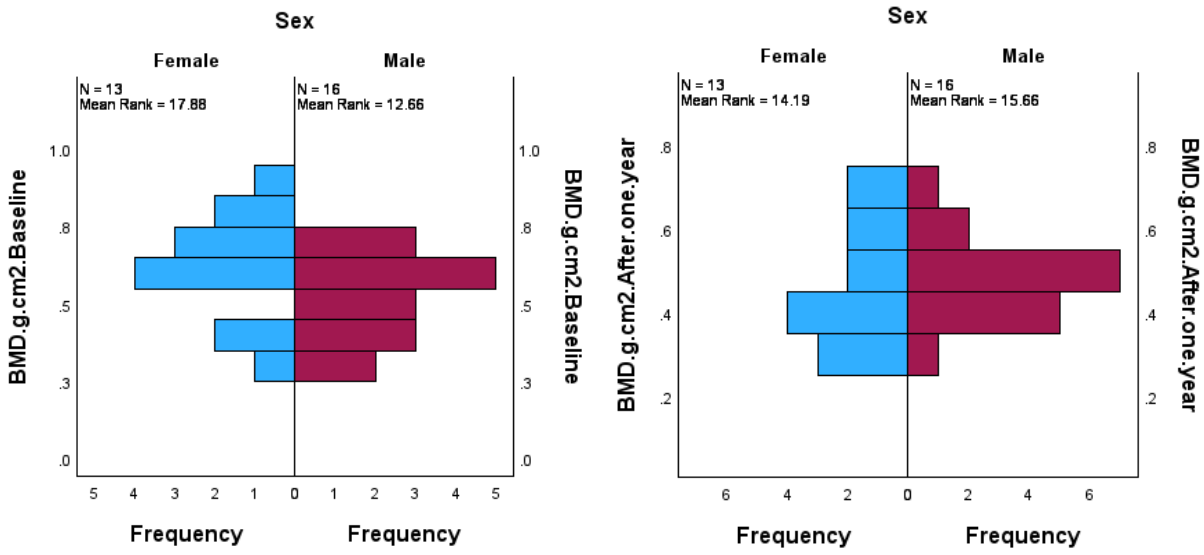

Figure III: Baseline and after one year bone mineral density (BMD) according to sex.

Figure IV illustrates that supplementation significantly increases serum calcium level among boys and girls over the period of one year in this population.

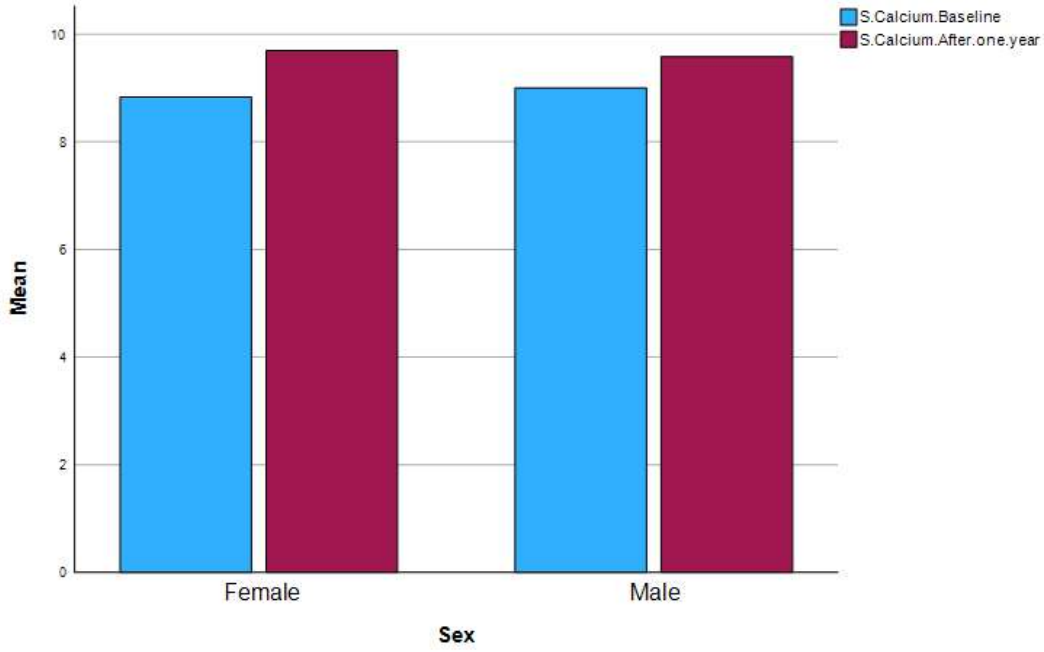

Figure IV: Baseline and after one year serum calcium level categorized by sex.

Figure V illustrates that supplementation significantly increases 25-OH vitamin D level among boys and girls over the period of one year in this population.

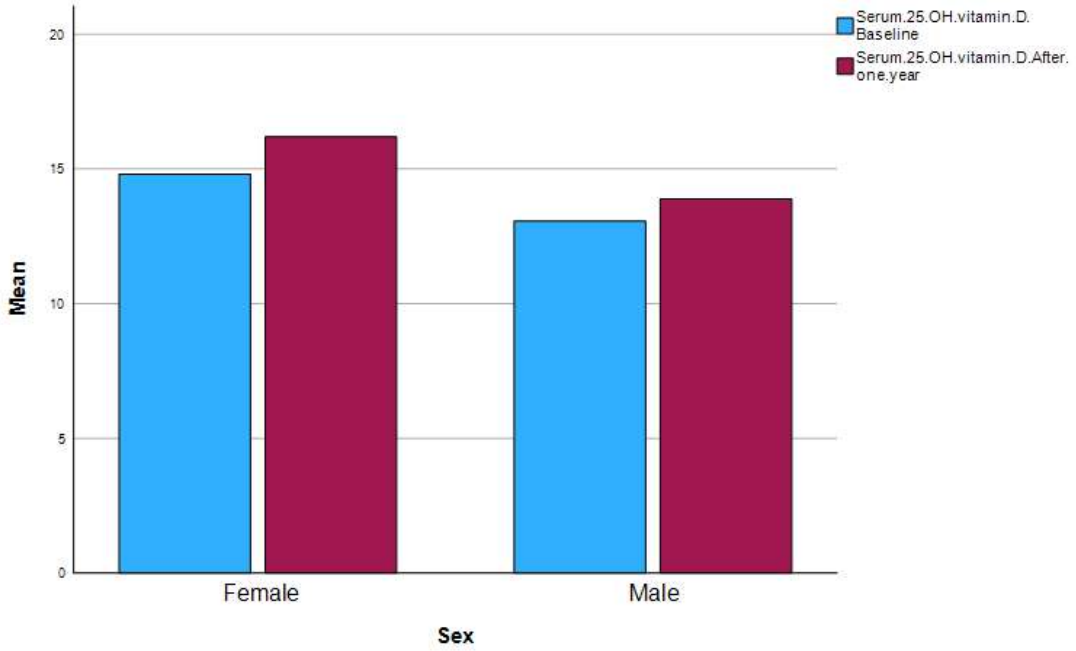

Figure V: Baseline and after one year serum 25-OH vitamin D level categorized by sex.

Figure VI *illustrates an increase in Serum PTH levels over the one-year period, attributed to the impact of supplementation.*

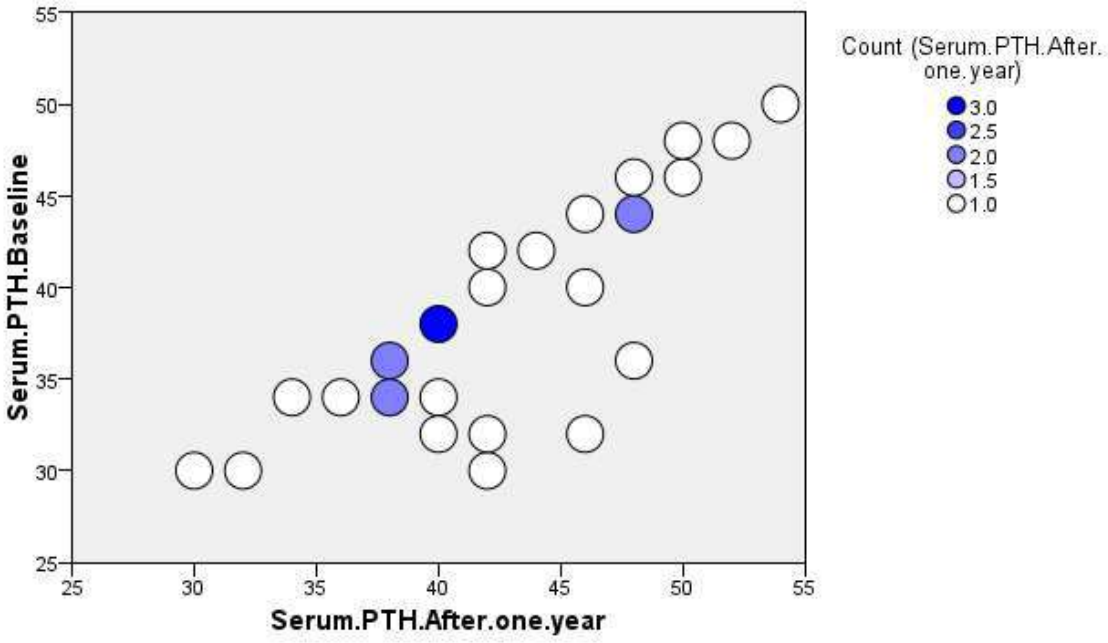

Figure VI: Baseline and after one one-year Serum PTH level.

Figure VII illustrates the flow of an increase in Serum Phosphate levels over the one-year period, attributed to the impact of supplementation.

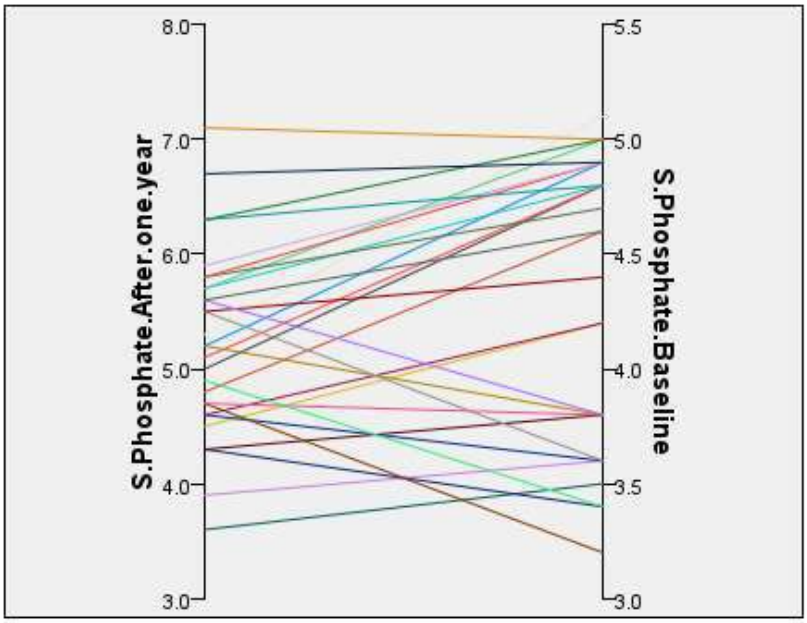

Figure VII: Changes in Serum Phosphate levels over a one-year duration.

Socio-demographic characteristics of studied children according to vitamin D insufficiency and deficiency are presented in ***Table II.***

Table II: Socio-demographic characteristics of studied children accordion to Vitamin D insufficiency and deficiency.

Variable	Total studied children *n*=29	Vitamin D insufficiency baseline *n*=29	Vitamin D deficiency baseline *n*=29
Residence:			
Rural, *n* (%)	4 (13.8%)	1 (3%)	1 (3%)
Urban, *n* (%)	25 (86.2%)	8 (28%)	11 (38%)
Sex:			
Boys, *n* (%)	16 (55.2%)	6 (21%)	9 (31%)
Girls, *n* (%)	13 (44.8%)	3 (10%)	3 (10%)
Education:			
Father, *n* (%)			
Illiterate	1 (3.4%)		
Intermediate	12 (41.4%)		4 (14%)
Primary	5 (17.2%)	2 (7%)	3 (10%)
Secondary	7 (24.1%)	1 (3%)	1 (3%)
University	4 (13.8%)	6 (21%)	4 (14%)
Mother, *n* (%)			
Illiterate	0 (0%)		
Intermediate	13 (44.8%)	1 (3%)	3 (10%)
Primary	5 (17.2%)	2 (7%)	1 (3%)
Secondary	8 (27.6%)	1 (3%)	4 (14%)
University	3 (10.3%)	5 (17%)	4 (14%)

Household Income:			
Income of Father, *n* (%)			
<15,000	8 (27.6%)	5 (17%)	4 (14%)
15,000 – 25,000	10 (34.5%)	1 (3%)	5 (17%)
>25,000	11 (37.9%)	3 (10%)	3 (10%)
Income of Mother, *n* (%)			
<15,000	19 (65.5%)	6 (21%)	8 (28%)
15,000 – 25,000	5 (17%)	1 (3%)	3 (10%)
>25,000	5 (17.2%)	2 (7%)	1 (3%)

In this study, we observed a higher prevalence of thalassemia among children in urban areas, with 25 cases (86.2%) in urban areas and 4 cases (13.8%) in rural areas. In the urban cohort, 28% exhibited vitamin D insufficiency and 38% had vitamin D deficiency at baseline, while in the rural group, only 3% had vitamin D insufficiency and deficiency. Furthermore, the study revealed that boys were more affected by thalassemia and demonstrated higher rates of both vitamin D insufficiency (21%) and deficiency (31%) than girls, where 10% exhibited vitamin D insufficiency and deficiency.

DISCUSSION

Children with thalassemia are at a high risk of osteoporosis, and any intervention aimed at enhancing bone health can help prevent fractures and related complications. This study demonstrated that vitamin D and calcium supplementation significantly enhanced bone mineral content (BMC) and bone mineral density (BMD), as well as serum *25(OH)D* and calcium levels without adverse effects. Notably, this study revealed a 71% prevalence of low bone mass, defined as a BMC Z-score of ≥ –2 [15, 16], compared to 50-64% in prior studies [9, 10]. This variance may be attributed to the reduced occurrence of malnutrition and improved thalassemia care in high-income nations.

Previous interventional studies have primarily employed bisphosphonates, in combination with calcium and vitamin D, to treat low bone mass in thalassemia patients, which yielded positive results for bone health [17, 18]. In contrast, our study used only oral vitamin D and calcium supplementation, potentially representing a safer and more cost-effective approach. The high prevalence of vitamin D deficiency in children with thalassemia can be attributed to factors such as liver iron deposition, reduced exposure to sunlight, and decreased physical activity owing to the burden of the disease [19].

While bone turnover markers are valuable for osteoporosis management [20], we did not observe a significant reduction in these markers, possibly because of the limited sample size in our study for these parameters. A potential limitation of this study is the absence of unsupplemented control subjects. However, the substantial decrease in the proportion of children with low BMC and BMD-Z scores (adjusted for age and height) with supplementation suggests that the increase in BMC is unlikely to be solely attributable to growth-related mineralization. Even at the conclusion of the study, many children exhibited low bone mass and vitamin D insufficiency, underscoring the need for further controlled trials to optimize the dosage of vitamin D and calcium

supplementation for osteoprotection in children with thalassemia.

CONCLUSION

Supplementation with oral vitamin D and calcium has been found to improve bone mineral content in children with thalassemia over a one-year period. This study suggests that these supplements may be beneficial for enhancing bone health in this population. Thalassemia is a genetic disorder that can lead to bone abnormalities and low bone mineral density. The researchers conducted a study involving children diagnosed with thalassemia, and the results showed that supplementation significantly increased bone mineral content. This finding is important because it highlights a potential intervention to improve bone health in children with thalassemia. It is worth noting that this study focused on oral vitamin D and calcium supplements, and further research is needed to determine the optimal dosage and duration of supplementation. Nonetheless, these findings provide promising evidence of the potential benefits of these supplements in enhancing bone health in children with thalassemia.

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