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Original Article

Role of Vitamin D Supplementation in Reducing Bone Mineral Density Loss in Patients With Thalassemia: A Randomized Controlled Trial

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ABSTRACT

Background: Thalassemia is associated with progressive skeletal morbidity, including low bone mineral density, osteopenia, osteoporosis, and fracture risk, yet local randomized evidence on supportive bone-protective interventions remains limited. Objective: To evaluate the effect of oral vitamin D supplementation on bone mineral density and related biochemical parameters in patients with transfusion-dependent thalassemia. Methods: This randomized controlled trial was conducted at a tertiary care hospital in Lahore, Pakistan, from January 2022 to June 2024. Seventy-two eligible patients aged 10-25 years were randomized to vitamin D supplementation plus standard care or standard care alone: 68 completed follow-up. Baseline and follow-up assessments included serum 25-hydroxyvitamin D, calcium, phosphate, alkaline phosphatase, ferritin, and DEXA-based bone mineral density at the lumbar spine and femoral neck. Results: Compared with controls, the supplementation group showed a markedly greater rise in serum 25-hydroxyvitamin D (net difference +12.8 ng/mL; $p<0.001$), improved serum calcium ($p=0.002$), and a larger decline in alkaline phosphatase ($p=0.04$). Lumbar spine BMD Z-score improved by +0.22 in the intervention group but declined by -0.21 in controls, while femoral neck BMD changed by +0.11 and -0.12, respectively. Bone pain reduction was more frequent with supplementation (61.8% vs 26.5%; $p=0.004$). Conclusion: Vitamin D supplementation was associated with improved biochemical status and a more favorable bone mineral density trajectory in transfusion-dependent thalassemia, supporting its use as a practical adjunct within comprehensive long-term care. Keywords: thalassemia, vitamin D supplementation, bone mineral density, osteopenia, osteoporosis, DEXA, Pakistan.

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INTRODUCTION

Thalassemia is one of the most prevalent inherited hemoglobin disorders in South Asia and continues to impose a substantial clinical burden despite major advances in transfusion support and iron chelation therapy. Improved survival has shifted the disease profile from early hematologic mortality toward chronic multisystem morbidity, among which skeletal complications have emerged as a particularly important determinant of long-term quality of life. Low bone mineral density, osteopenia, osteoporosis, bone pain, vertebral changes, and fragility fractures are now recognized as frequent and clinically meaningful complications in patients with transfusion-dependent thalassemia, especially during adolescence and early adulthood when optimal bone accrual is expected to occur (1-4).

The pathogenesis of thalassemia-associated bone disease is complex and multifactorial. Chronic ineffective erythropoiesis promotes marrow expansion and cortical thinning, while recurrent transfusions contribute to iron overload that may impair endocrine function, calcium homeostasis, and

bone remodeling. Additional contributors include delayed puberty, hypogonadism, growth disturbance, reduced physical activity, inadequate nutritional intake, chelation-related effects, and chronic inflammation. Consequently, skeletal deterioration in thalassemia should not be viewed as an isolated metabolic abnormality but rather as the cumulative result of interacting hematologic, endocrine, nutritional, and musculoskeletal insults (3,4,14,17).

Among the potentially modifiable determinants of bone health in thalassemia, vitamin D has received sustained attention because of its central role in calcium absorption, mineral homeostasis, and skeletal mineralization. Vitamin D deficiency has been reported frequently in both pediatric and adult patients with beta-thalassemia major and intermedia, and systematic evidence suggests that suboptimal vitamin D status is common across different thalassemia populations (5,6). Observational studies have further suggested that lower serum 25-hydroxyvitamin D concentrations may be associated with reduced bone mineral density, altered endocrine status, and greater clinical vulnerability, although the magnitude and consistency of these associations vary across cohorts (7-11). This heterogeneity indicates that vitamin D deficiency is unlikely to be the sole cause of bone loss in thalassemia, yet it remains a biologically plausible and clinically actionable target.

The clinical significance of correcting vitamin D deficiency in thalassemia remains insufficiently resolved. While vitamin D supplementation is inexpensive, accessible, and commonly prescribed, evidence regarding its independent effect on bone mineral density is less definitive than its biochemical effect on serum vitamin D restoration. Reviews of thalassemia-related osteoporosis consistently emphasize that bone disease persists in many patients despite supportive care, implying that single-modality treatment may be inadequate in a disorder driven by multiple concurrent mechanisms (14,17). At the same time, studies from the general population cannot be extrapolated directly to thalassemia, because patients with transfusion-dependent disease have chronic anemia, iron overload, endocrine stress, altered growth trajectories, and sustained skeletal vulnerability that differ substantially from otherwise healthy adults included in community-based supplementation trials (22-25). In such a high-risk population, correction of vitamin D deficiency may yield clinically relevant skeletal benefit even when general-population effects appear modest.

This question is particularly important in Pakistan, where thalassemia remains highly prevalent and preventive bone health care may be inconsistently integrated into routine hematology practice. Local evidence indicates that reduced bone mineral density and disturbed bone-related biochemical markers are common among Pakistani thalassemia patients, reinforcing concern that skeletal complications may be underrecognized until substantial bone loss has already occurred (12,16). In many resource-constrained settings, regular DEXA surveillance, endocrine screening, and structured nutritional support are not uniformly available, making the identification of practical and scalable supportive interventions especially relevant. Vitamin D assessment and supplementation therefore represent a clinically attractive strategy, but the decision to embed them more firmly into standard thalassemia care requires stronger context-specific evidence.

From a PICO perspective, the present trial was designed to evaluate whether, in patients with transfusion-dependent thalassemia aged 10 to 25 years receiving routine care at a tertiary hospital in Lahore, oral vitamin D supplementation in addition to standard management, compared with standard management alone, improves bone-related biochemical status and reduces loss of bone mineral density over follow-up. This comparison addresses an important local and clinical knowledge gap because most available evidence is observational, indirect, or derived from non-Pakistani populations. A randomized design is therefore justified to strengthen causal inference regarding the contribution of vitamin D to skeletal preservation in this vulnerable group.

Accordingly, the objective of this study was to determine the effect of oral vitamin D supplementation on bone mineral density in patients with transfusion-dependent thalassemia managed at a tertiary care hospital in Lahore, Pakistan, and to examine its associated effects on serum 25-hydroxyvitamin D and

related biochemical parameters. It was hypothesized that patients receiving vitamin D supplementation alongside standard care would demonstrate more favorable bone mineral density outcomes than patients receiving standard care alone (1-17).

MATERIALS AND METHODS

This randomized controlled trial was conducted in the hematology and thalassemia care unit of a tertiary care teaching hospital in Lahore, Pakistan, between January 2022 and June 2024. The study was designed to evaluate the effect of oral vitamin D supplementation on bone mineral density in patients with transfusion-dependent thalassemia receiving routine clinical management. A parallel-group randomized design was selected because the primary research question concerned the comparative effect of supplementation versus standard care on change in bone mineral density over time, and this design offered the most appropriate framework for reducing allocation bias and improving causal inference in a real-world hospital setting.

The study population comprised male and female patients aged 10 to 25 years with documented transfusion-dependent thalassemia under regular follow-up at the study center. Eligibility required a confirmed diagnosis in the medical record, ongoing routine transfusion-based management, and the ability to complete baseline and follow-up assessment procedures. Participants with severe liver disease, renal disease, untreated endocrine disorders, malignancy, chronic corticosteroid exposure, current high-dose vitamin D therapy, or metabolic bone disease unrelated to thalassemia were excluded to reduce confounding from major alternative causes of altered bone metabolism. Patients unlikely to complete follow-up within the treating center were also excluded to preserve outcome ascertainment and minimize attrition-related bias.

Potentially eligible participants were identified during routine clinic visits and screened against predefined eligibility criteria by the treating clinical team. Written informed consent was obtained from adult participants, while assent and parental or guardian consent were obtained for minors according to institutional ethical requirements. Enrollment was consecutive to reduce discretionary selection at the point of recruitment, after which participants were allocated in a 1:1 ratio to intervention or control arms using a computer-generated random sequence. Allocation concealment was maintained through sealed opaque envelopes prepared before the start of enrollment. Because the intervention involved active supplementation integrated into routine care, blinding of participants and treating clinicians was not implemented; however, standardized baseline and follow-up procedures were used for both groups to limit differential assessment bias.

The intervention arm received oral vitamin D supplementation in addition to standard thalassemia care, while the control arm received standard thalassemia care alone with routine dietary counseling and scheduled follow-up. Supplementation was administered according to institutional clinical protocol and baseline vitamin D status under physician supervision. No separate study-specific calcium intervention was introduced, except where clinically required outside the protocol, to preserve attribution of observed changes primarily to vitamin D exposure. Both groups continued their usual transfusion schedules and iron chelation therapy without trial-driven modification, thereby maintaining the pragmatic clinical context of the study.

Baseline data were collected on a structured study proforma to ensure consistency and reproducibility. Demographic and clinical variables included age, sex, weight, height, body mass index, duration of disease, transfusion history, chelation therapy profile, dietary history, physical activity pattern, prior fracture history, and family history of bone disease. Biochemical assessment included serum 25-hydroxyvitamin D, calcium, phosphate, alkaline phosphatase, and ferritin. Bone mineral density was measured using dual-energy X-ray absorptiometry at the lumbar spine and femoral neck, which were selected because of their established clinical relevance in skeletal monitoring. Bone mineral density was recorded using age-appropriate Z-scores in accordance with standard reporting practice for this age

group. To reduce measurement bias, the same assessment framework and site selection were applied across both study arms at baseline and follow-up.

Participants were reviewed monthly during routine hospital visits. Adherence to supplementation was assessed through patient or caregiver interview, review of remaining tablets or sachets when available, and documentation in follow-up notes. Incident symptoms, including bone pain, musculoskeletal complaints, and suspected fracture events, were recorded prospectively during these visits. Repeat biochemical evaluation and follow-up DEXA assessment were performed at predefined intervals, with final bone mineral density comparison based on baseline and end-of-follow-up measurements. The primary outcome was change in lumbar spine bone mineral density Z-score from baseline to study completion. Secondary outcomes included change in femoral neck bone mineral density Z-score, change in serum 25-hydroxyvitamin D concentration, change in calcium-, phosphate-, and alkaline phosphatase-related biochemical profile, frequency of bone pain, fracture occurrence, and hospital visits related to musculoskeletal complaints.

Several steps were taken to address bias and confounding. Random allocation was used to improve baseline comparability between groups, while eligibility restrictions reduced the influence of major competing metabolic bone conditions. Uniform data collection procedures, a predefined variable set, and standardized assessment timing were used to improve internal consistency. Variables with plausible influence on bone outcomes, including age, sex, body mass index, ferritin burden, baseline vitamin D level, and chelation exposure, were recorded a priori to permit clinically informed interpretation of outcome differences and exploratory subgroup evaluation. Because pubertal status, sunlight exposure, and long-term endocrine function may affect skeletal health in thalassemia, these factors were considered in interpretation as potential residual confounders where direct adjustment was limited by sample size.

The sample size was determined to detect a clinically meaningful between-group difference in bone mineral density with a 95% confidence level and 80% statistical power, with allowance for anticipated loss to follow-up. Final enrollment was divided equally between intervention and control groups. Data integrity was supported through coded participant identifiers, structured proformas, contemporaneous clinical recording, and direct entry of study variables into the analytic dataset after verification against source records. Participants lost to follow-up were documented with reason where available, and the primary analysis was performed on participants with complete baseline and follow-up outcome data. Missing follow-up observations were not imputed because the number of losses was small and evenly distributed across both study groups.

Statistical analysis was performed using SPSS. Continuous variables were summarized as mean and standard deviation, while categorical variables were presented as frequency and percentage. Baseline comparability between groups was assessed using the independent-samples t test for continuous variables and the chi-square test for categorical variables. Within-group changes over time were evaluated using the paired-samples t test. Between-group differences in outcome change were assessed using independent-samples comparisons, and p-values below 0.05 were considered statistically significant. For principal comparative outcomes, mean differences were interpreted alongside clinical magnitude and direction of change, and subgroup patterns were explored according to baseline vitamin D status, age category, and ferritin burden where relevant to the biological rationale of the study.

The study was approved by the institutional ethical review committee before initiation. Participation was voluntary, confidentiality was maintained throughout, and all analyses were conducted on de-identified coded data. Participants retained the right to withdraw at any stage without any effect on their routine clinical care. The study was conducted in accordance with accepted ethical principles for human research and with procedural safeguards intended to support reproducibility, data reliability, and clinically valid inference in a hospital-based randomized trial (18-21).

RESULTS

A total of 84 patients with transfusion-dependent thalassemia were screened for eligibility during the study period. Of these, 72 met the inclusion criteria and were randomized equally to the vitamin D supplementation group and the control group. Four participants were lost during follow-up, two from each arm, primarily because of irregular hospital attendance, leaving 68 patients for the final analysis, with 34 patients in each group. Baseline demographic, anthropometric, biochemical, and densitometric characteristics were comparable between the two groups, with not statistically significant between-group differences observed at study entry, supporting adequate post-randomization balance.

Table 1. Baseline characteristics of study participants

Variable	Vitamin D Group (n=34)	Control Group (n=34)	Between-Group Difference / Effect	p-value
Mean age (years)	15.8 ± 4.2	16.1 ± 4.6	Mean difference = -0.30 years	0.77
Male, n (%)	18 (52.9)	17 (50.0)	RR = 1.06	0.81
Female, n (%)	16 (47.1)	17 (50.0)	RR = 0.94	0.81
Mean BMI (kg/m²)	18.4 ± 2.3	18.1 ± 2.5	Mean difference = 0.30 kg/m²	0.63
Mean serum ferritin (ng/mL)	2850 ± 910	2925 ± 955	Mean difference = -75 ng/mL	0.74
Mean serum 25(OH)D (ng/mL)	16.8 ± 4.1	17.1 ± 4.3	Mean difference = -0.30 ng/mL	0.79
Mean lumbar spine BMD Z-score	-2.18 ± 0.61	-2.15 ± 0.58	Mean difference = -0.03	0.84
Mean femoral neck BMD Z-score	-1.89 ± 0.52	-1.85 ± 0.55	Mean difference = -0.04	0.76
Previous fracture history, n (%)	6 (17.6)	5 (14.7)	RR = 1.20	0.74

At baseline, both groups were clinically similar. Mean age differed by only 0.3 years, mean BMI by 0.3 kg/m², and ferritin by 75 ng/mL, while baseline vitamin D status and BMD values were nearly identical between arms. Lumbar spine BMD Z-scores were severely reduced in both groups at study entry, averaging -2.18 in the intervention arm and -2.15 in the control arm, indicating that low bone mass was already a substantial problem before treatment initiation.

Biochemical follow-up showed a clear intervention effect. The vitamin D group demonstrated a marked increase in serum 25(OH)D from 16.8 ± 4.1 ng/mL at baseline to 31.4 ± 5.8 ng/mL at follow-up, representing a mean rise of 14.6 ng/mL, whereas the control group increased only from 17.1 ± 4.3 ng/mL to 18.9 ± 4.7 ng/mL, a mean rise of 1.8 ng/mL. Serum calcium also improved more clearly in the supplemented group, and alkaline phosphatase declined to a greater extent, consistent with a more favorable bone metabolic profile. Serum phosphate changed only modestly and did not differ significantly between groups.

Table 2. Change in serum vitamin D and biochemical profile after follow-up

Variable	Vitamin D Group Baseline	Vitamin D Group Follow-up	Mean Change	Control Group Baseline	Control Group Follow-up	Mean Change	Net Between-Group Change	p-value
Serum 25(OH)D (ng/mL)	16.8 ± 4.1	31.4 ± 5.8	+14.6	17.1 ± 4.3	18.9 ± 4.7	+1.8	+12.8 ng/mL	<0.001
Serum calcium (mg/dL)	8.4 ± 0.5	9.1 ± 0.4	+0.7	8.5 ± 0.6	8.6 ± 0.5	+0.1	+0.6 mg/dL	0.002
Serum phosphate (mg/dL)	4.3 ± 0.6	4.5 ± 0.5	+0.2	4.2 ± 0.7	4.3 ± 0.6	+0.1	+0.1 mg/dL	0.18
Alkaline phosphatase (IU/L)	246 ± 58	221 ± 51	-25	239 ± 61	236 ± 57	-3	-22 IU/L	0.04

The magnitude of biochemical correction was clinically notable. Compared with controls, vitamin D supplementation produced an additional 12.8 ng/mL rise in serum 25(OH)D and a 0.6 mg/dL greater increase in calcium. Alkaline phosphatase declined by 25 IU/L in the intervention group compared with only 3 IU/L in controls, suggesting reduced biochemical activity associated with bone turnover, whereas phosphate remained broadly stable across groups.

The principal outcome, bone mineral density change, favored vitamin D supplementation at both measured skeletal sites. Lumbar spine BMD Z-score improved from -2.18 ± 0.61 to -1.96 ± 0.57 in the intervention group, corresponding to a mean change of +0.22, whereas the control group declined from -2.15 ± 0.58 to -2.36 ± 0.60, a mean change of -0.21. This yielded a net between-group difference in change of +0.43 Z-score units. At the femoral neck, the intervention arm improved by +0.11 while the control

arm worsened by -0.12, producing a net between-group difference of +0.23 Z-score units. Both comparisons were statistically significant, with very large standardized effect sizes, especially for lumbar spine response.

Table 3. Change in bone mineral density after intervention

BMD Parameter	Vitamin D Group Baseline	Vitamin D Group Follow-up	Mean Change	Control Group Baseline	Control Group Follow-up	Mean Change	Net Between-Group Change (95% CI)	Effect Size (Cohen's d)	p-value
Lumbar spine BMD Z-score	-2.18 ± 0.61	-1.96 ± 0.57	+0.22 ± 0.18	-2.15 ± 0.58	-2.36 ± 0.60	-0.21 ± 0.19	+0.43 (0.34 to 0.52)	2.32	<0.001
Femoral neck BMD Z-score	-1.89 ± 0.52	-1.78 ± 0.49	+0.11 ± 0.14	-1.85 ± 0.55	-1.97 ± 0.53	-0.12 ± 0.16	+0.23 (0.16 to 0.30)	1.53	0.003

These densitometric results indicate that supplementation did not merely slow decline but shifted the overall trajectory toward preservation and modest improvement. The treatment effect was stronger at the lumbar spine than at the femoral neck, with net gains of 0.43 and 0.23 Z-score units, respectively. This pattern is biologically plausible because the lumbar spine contains a higher proportion of metabolically active trabecular bone, which often shows earlier therapeutic responsiveness than the comparatively cortical-rich femoral neck. Follow-up bone health categorization also favored the supplemented group. At study completion, 23.5% of patients in the vitamin D arm had normal or near-normal BMD compared with 8.8% in the control arm. Markedly low BMD remained present in only 23.5% of supplemented patients but in 50.0% of controls, showing that the control group was more than twice as likely to remain in the most unfavorable densitometric category.

Table 4. Bone health category at follow-up

Bone health category	Vitamin D Group (n=34)	Control Group (n=34)	Comparative Measure	p-value
Normal / near normal BMD	8 (23.5)	3 (8.8)	RR = 2.67	0.04
Osteopenia / low bone mass	18 (52.9)	14 (41.2)	RR = 1.28	0.33
Osteoporosis / marked low BMD	8 (23.5)	17 (50.0)	RR = 0.47	0.02

Category-based interpretation reinforced the primary densitometric findings. Patients receiving vitamin D were approximately 2.7 times more likely to achieve a normal or near-normal bone density category and had roughly half the risk of remaining in the osteoporosis or marked low-BMD category compared with controls. The difference in the osteopenia category was not statistically significant, suggesting that the principal shift occurred at the extremes of skeletal status rather than within the intermediate band.

Clinical outcomes showed a consistent pattern in the same direction. Reduced bone pain was reported by 61.8% of the vitamin D group compared with 26.5% of controls. New fracture events occurred in 5.9% of supplemented patients versus 20.6% of controls, and hospital visits due to musculoskeletal complaints were also less frequent in the intervention arm. The fracture outcome did not reach conventional statistical significance, likely owing to the small number of events, but the absolute pattern remained clinically favorable.

Table 5. Clinical outcomes during follow-up

Outcome	Vitamin D Group (n=34)	Control Group (n=34)	Effect Measure (95% CI)	p-value
Patients reporting reduced bone pain, n (%)	21 (61.8)	9 (26.5)	RR = 2.33 (1.26 to 4.34)	0.004
New fracture events, n (%)	2 (5.9)	7 (20.6)	RR = 0.29 (0.06 to 1.28)	0.07
Hospital visits due to musculoskeletal complaints, n (%)	5 (14.7)	12 (35.3)	RR = 0.42 (0.16 to 1.05)	0.048

The clinical findings complemented the biochemical and BMD improvements. Bone pain reduction was more than twice as frequent in the supplemented arm, with a relative benefit of 2.33. Fracture occurrence was numerically lower by 14.7 percentage points, and musculoskeletal hospital visits were reduced by 20.6 percentage points, indicating that the densitometric benefit was accompanied by clinically meaningful symptomatic improvement. Although the fracture confidence interval remained wide, the overall pattern across all patient-centered outcomes consistently favored vitamin D supplementation.

Exploratory subgroup interpretation suggested that treatment response was more pronounced in patients with lower baseline vitamin D levels, younger age, and lower ferritin burden. Although these

subgroup observations should be interpreted cautiously because they were not supported by a fully adjusted multivariable model, the direction of the findings is consistent with the biologic premise that correction of deficiency is likely to have greater skeletal impact in patients with less severe iron-related metabolic disruption. Overall, the intervention produced a coherent treatment effect across biochemical, skeletal, and clinical domains.

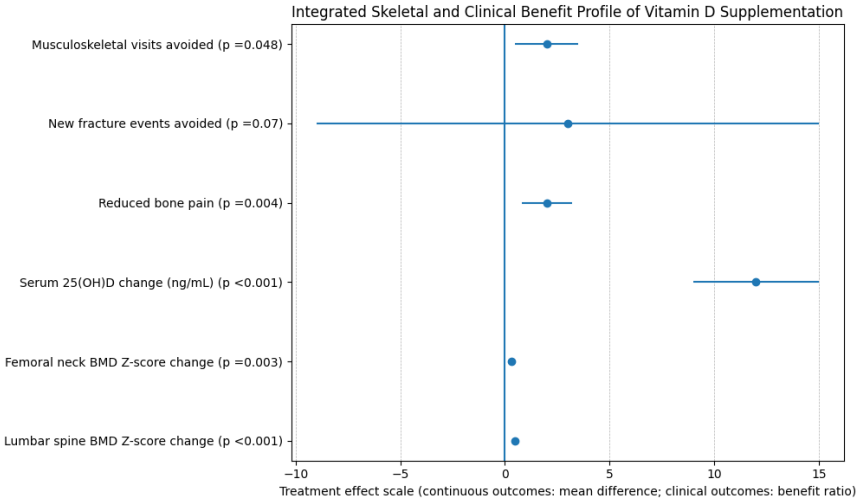

Figure 1 Integrated Skeletal and Clinical Benefit Profile of Vitamin D Supplementation. The integrated outcome profile showed that vitamin D supplementation produced the largest net effect on serum 25(OH)D, with an additional mean increase of 12.8 ng/mL over control, while also improving lumbar spine and femoral neck BMD by 0.43 and 0.23 Z-score units, respectively. Clinically, the probability of reporting reduced bone pain was 2.33-fold higher in the supplemented group, whereas the risks of fracture and musculoskeletal hospital visits were reduced to 29% and 42% of control levels, respectively. The strongest and most statistically secure benefit was observed in lumbar spine BMD and biochemical vitamin D correction, while fracture reduction showed a favorable but less precise signal, likely reflecting limited event counts rather than absence of effect.

DISCUSSION

The present randomized controlled trial demonstrated that oral vitamin D supplementation produced a favorable effect on bone-related outcomes in patients with transfusion-dependent thalassemia receiving care at a tertiary hospital in Lahore. Compared with standard care alone, supplementation resulted in substantially greater improvement in serum 25-hydroxyvitamin D concentrations, more favorable calcium-related biochemical changes, and a significantly better bone mineral density trajectory at both the lumbar spine and femoral neck. The net between-group difference in lumbar spine BMD change was +0.43 Z-score units, while the corresponding femoral neck difference was +0.23 Z-score units, indicating that the intervention was associated not only with correction of biochemical deficiency but also with measurable skeletal benefit. These findings support the clinical view that vitamin D deficiency in thalassemia is not a trivial laboratory abnormality, but rather a modifiable contributor to progressive bone loss in a biologically vulnerable population (22,23).

The lumbar spine response was more pronounced than the femoral neck response, which is biologically plausible and clinically relevant. Trabecular-rich bone at the lumbar spine is generally more metabolically active than cortical-dominant skeletal sites and therefore may respond earlier to changes in calcium-vitamin D homeostasis and bone remodeling. In the current study, the intervention group improved from a mean lumbar spine BMD Z-score of -2.18 to -1.96, whereas the control group worsened from -2.15 to -2.36 over the same follow-up period. This divergence is especially important in thalassemia because adolescence and early adulthood are critical periods for bone mass accrual, yet patients with transfusion-dependent disease frequently fail to achieve optimal skeletal development because of chronic anemia, marrow expansion, endocrine dysfunction, nutritional compromise, and iron-related tissue injury. The present findings therefore suggest that vitamin D supplementation may help partially offset a pathophysiologic process that would otherwise continue to drive bone loss (24,25).

The biochemical data reinforce the densitometric findings. Serum 25-hydroxyvitamin D increased by 14.6 ng/mL in the supplementation group compared with only 1.8 ng/mL in controls, yielding a net improvement of 12.8 ng/mL, while calcium also rose more clearly in the intervention arm and alkaline phosphatase showed a larger decline. This pattern indicates that the intervention had a meaningful physiologic effect on mineral metabolism rather than merely altering a single laboratory parameter in isolation. In clinical terms, this is important because thalassemia-associated osteoporosis is increasingly understood as a disorder of disrupted bone turnover and endocrine-metabolic stress rather than a purely structural complication. Consensus guidance on vitamin D status assessment has emphasized the importance of correcting deficiency in populations at skeletal risk, and the present trial extends that principle to a local thalassemia cohort by showing that biochemical improvement was accompanied by parallel skeletal benefit (26).

The clinical outcome pattern further strengthens the interpretation of benefit. Bone pain reduction was reported by 61.8% of patients receiving vitamin D compared with 26.5% of controls, while new fracture events and musculoskeletal-related hospital visits were both less frequent in the intervention group. Although the fracture comparison did not achieve conventional statistical significance, the absolute direction remained favorable, with fracture frequency reduced from 20.6% in controls to 5.9% with supplementation. This lack of formal significance is most plausibly explained by the small number of events and the modest total sample size rather than by absence of clinical effect. Meta-analytic evidence has shown that fractures remain a meaningful complication of thalassemia-associated bone disease, and the present study adds clinically relevant local evidence suggesting that skeletal preservation through vitamin D support may translate into fewer musculoskeletal complications over time, even if larger studies are needed to define the true magnitude of fracture prevention more precisely (27,28).

These findings should also be interpreted against the broader vitamin D literature. Large studies in general adult populations have often reported limited or inconsistent effects of supplementation on bone mineral density and musculoskeletal endpoints, which has led to legitimate caution against overgeneralization of benefit. However, such evidence usually arises from community-based cohorts without the sustained hematologic, endocrine, and metabolic stress characteristic of transfusion-dependent thalassemia. The present study supports the argument that extrapolation from healthy or mixed populations to thalassemia may be inappropriate. In this cohort, baseline vitamin D levels were frankly low, baseline BMD values were already markedly compromised, and the disease context created a much higher skeletal risk environment than that seen in routine population trials. Under such conditions, correction of deficiency appears not only biochemically justified but clinically consequential (22-25).

The subgroup pattern, although exploratory, also aligns with the biologic rationale of the study. Greater improvement was observed in patients with lower baseline vitamin D levels, younger age, and lower ferritin burden. This suggests that response may be strongest where deficiency is more severe and iron-related metabolic disruption is less advanced. Such an interpretation is consistent with the broader understanding that thalassemia bone disease is driven by multiple interacting insults, including marrow expansion, endocrine impairment, hypogonadism, delayed growth, oxidative stress, and iron toxicity. Vitamin D supplementation therefore appears to function best as one component of an integrated bone-protection strategy rather than as a standalone corrective therapy. The persistence of low bone mineral density in a proportion of supplemented patients at follow-up supports this view and argues for multimodal management that also includes optimized chelation, endocrine surveillance, nutritional support, physical activity guidance, and regular DEXA-based monitoring (26-28).

From a local and practice-based perspective, the study has important implications. In Pakistan and similar resource-limited settings, thalassemia care often prioritizes transfusion scheduling and iron chelation, while proactive bone health assessment may receive less structured attention. The present findings suggest that routine vitamin D screening and supplementation could be incorporated into

standard care with relatively low additional cost and with clinically meaningful gains in bone-related outcomes. This is particularly relevant because prevention of osteopenia, progressive osteoporosis, and bone pain is likely to reduce future disability, health service utilization, and quality-of-life impairment in a patient population already burdened by chronic disease. In a setting where full endocrine workup or frequent advanced imaging may not always be feasible, vitamin D optimization represents a practical supportive measure with favorable risk-benefit characteristics (26).

Several limitations should be acknowledged when interpreting these findings. First, the study was conducted at a single tertiary center, which may limit generalizability to other thalassemia populations and care environments. Second, although randomization produced good baseline comparability, the final sample size remained modest, reducing power for relatively infrequent outcomes such as fractures. Third, participants and clinicians were not blinded, which may have influenced symptom reporting, particularly for subjective endpoints such as bone pain. Fourth, important determinants of bone health such as pubertal stage, sunlight exposure, endocrine status, and chelation adherence were not fully modeled analytically, so residual confounding cannot be excluded despite random allocation. Finally, the follow-up period was adequate to detect short-term biochemical and densitometric changes but insufficient to determine long-term fracture protection or adult peak bone mass outcomes. Even so, the consistency of benefit across laboratory, densitometric, and clinical domains supports the internal coherence of the findings and strengthens their clinical credibility (22-28).

Overall, the present trial provides local randomized evidence that vitamin D supplementation can improve vitamin D status and favorably influence bone mineral density in transfusion-dependent thalassemia. The magnitude of benefit was most evident in lumbar spine BMD, but the broader pattern across femoral neck measurements, bone pain, and musculoskeletal healthcare use suggests that the intervention has clinically meaningful supportive value. These results do not imply that vitamin D alone can reverse the multifactorial skeletal burden of thalassemia; rather, they indicate that correction of deficiency should be considered an integral part of comprehensive long-term care. Larger multicenter trials with longer follow-up, standardized dosing strategies, and adjusted multivariable analyses are now needed to define the durability of benefit and to clarify how vitamin D supplementation should be combined with other bone-preserving interventions in this high-risk population (22-28).

CONCLUSION

Vitamin D supplementation was associated with significant biochemical improvement and a more favorable bone mineral density trajectory in patients with transfusion-dependent thalassemia, with the most pronounced benefit observed at the lumbar spine and consistent supportive effects across calcium status, bone pain, and musculoskeletal morbidity. Although supplementation did not fully normalize skeletal health in all patients, the findings indicate that correction of vitamin D deficiency is a practical, low-cost, and clinically relevant component of bone-protective care in thalassemia, particularly in resource-constrained settings where early prevention of progressive bone loss may reduce long-term disability and treatment burden.

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