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Evaluation of Vitamin D Status and Bone Mineral Density in Preschool Children with Fractures

Wafaa O. Ahmed[1], Walaa H. Ali[2], Hend M. Ahmed[3], Doaa Y. Hammad[4], Aliaa El Gendy[5], Amira Medhat[5], Eman Mohamed Elsayed[1]

[1]Department of Pediatrics, Ain Shams University, Cairo, Egypt; Wafaaosman83@med.asu.edu.eg, https://orcid.org/0000-0003-4081-0705; Iman.badawy@med.asu.edu.eg; https://orcid.org/0000-0003-2538-623X
[2]Child Health Department, National Research Centre, Dokki, Giza, Egypt; walaa.hani79@gmail.com; https://orcid.org/0000-0002-6917-0599
[3]Medical Biochemistry Department, National Research Centre, Dokki, Giza, Egypt; Hendbio30@yahoo.com; https://orcid.org/0009-0005-9624-1320
[4]Biological Anthropology Department, National Research Centre, Dokki, Giza, Egypt; vipdoaa@hotmail.com; https://orcid.org/0000-0002-4664-7622
[5]Complementary Medicine Department, National Research Centre, Dokki, Giza, Egypt; aliaaelgendy.nrc@hotmail.com, https://orcid.org/0000-0001-7130-7470; amira.medhat.phd@gmail.com, https://orcid.org/0000000313591164

ABSTRACT: Vitamin D is essential for calcium homeostasis and bone mineralization during childhood. However, the effectiveness of vitamin D supplementation in improving bone health and reducing fracture risk in children remains controversial. This study aimed to assess serum 25-hydroxyvitamin D [25(OH)D], vitamin D–binding protein (DBP), and calcium levels, as well as bone mineral density (BMD) in preschool children with fractures and evaluate the short-term effects of vitamin D supplementation. This cross-sectional study included 90 children aged 3–5 years, divided into the fracture (n=45) and control (n=45) groups. Serum 25(OH)D, calcium, and DBP levels were measured. BMD was assessed using dual-energy X-ray absorptiometry at the lumbar spine and femoral neck. Children in the fracture group received vitamin D_3 supplementation (600 IU/day) for 2 months, followed by reassessment. Statistical analyses included group comparisons, correlation, and regression models. Children with fractures had significantly lower serum 25(OH)D, calcium, and DBP levels compared to controls ($p<0.001$). No baseline differences in BMD were observed between groups. After supplementation, serum biomarkers and femoral neck BMD significantly improved ($p<0.001$), while lumbar spine BMD showed a significant but paradoxical decrease. Serum 25(OH)D, DBP, and lumbar spine Z-score were independent predictors of femoral neck BMD. Moreover, higher vitamin D levels and BMD were independently associated with a reduced fracture risk. Our findings demonstrated that vitamin D deficiency was strongly associated with fractures in preschool children, while supplementation improved biochemical markers and site-specific BMD. Thus, vitamin D status presents a key determinant of bone health and fracture risk in children.

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1. INTRODUCTION

Vitamin D is a secosteroid, fat-soluble prohormone that plays a crucial role in calcium absorption and bone mineralization, and it is also essential for immune system function (Bekas & Zafeiris, 2024). Vitamin D is synthesized cutaneously through ultraviolet B (UVB) radiation and is obtained from dietary sources or supplementation (Wacker & Holick, 2013; Na et al., 2022). Its two primary forms are Vitamin D_3, which is essential for animals and synthesized in the skin, and Vitamin D_2, which is produced by plants (Liu et al., 2025). The primary source of Vitamin D in humans is skin exposure to UVB radiation, and it can be obtained from limited dietary sources, such as egg yolks (Ismailova & White, 2022).

Vitamin D deficiency is a pervasive global public health challenge; it is particularly critical during childhood when rapid bone growth and mineralization demand optimal nutritional support. An estimated 30% of children worldwide have serum 25-hydroxyvitamin D [25(OH)D] levels below 20 ng/mL, a threshold linked to impaired calcium homeostasis, poor bone mineralization, and increased risk of rickets and fractures (Holick et al., 2011; Al-Shammari, 2025). Fractures in childhood may be a sign of underlying bone fragility, which could predict an increased risk of fractures during adulthood. Although vitamin D is essential for bone mineralization, its role in preventing fractures among children and adolescents remains undefined. Because vitamin D insufficiency is highly prevalent, investigating whether this insufficiency is associated with fractures in patients under 18 years old is necessary (Ganmaa et al., 2023).

In adults, vitamin D deficiency, along with low bone mineral density (BMD), has been linked to fracture risk. However, in children, fracture risk cannot be easily predicted, and whether low vitamin D levels are linked to why certain children experience fractures due to minor trauma whereas others do not remains unclear. Therefore, it is necessary to confirm the link between vitamin D levels and fractures, bone healing, and risk of refracture in children (Winzenberg et al., 2011a).

Optimizing BMD in children and adolescents is essential for the life-long prevention of osteoporosis and fractures (Yang et al., 2021; Herdea et al., 2023). Fractures are common in childhood, with approximately one-third of children experiencing at least one fracture before the age of 18 years, with peak incidence during the pubertal growth spurt. These injuries may result in temporary functional limitation and, in some cases, significant morbidity. While injury prevention is an important preventive strategy, improving bone strength during growth represents a complementary approach to reducing fracture risk (Winzenberg et al., 2018).

Observational studies have reported a high prevalence of vitamin D deficiency among children across different populations, with some studies suggesting an independent association between low vitamin D status and increased fracture risk. Vitamin D supplementation has received considerable attention regarding bone strengthening owing to its essential role in calcium absorption and bone mineralization. However, evidence from randomized controlled trials evaluating vitamin D supplementation for fracture prevention in children remains inconsistent (Winzenberg et al., 2018), and its effectiveness in improving child bone health remains controversial. While some randomized controlled trials have demonstrated that daily supplementation with 800–2000 IU of vitamin D_3 can improve BMD, particularly in the lumbar spine (L1–L4), other studies have reported minimal or no significant effects. These inconsistencies may be attributed to variations in baseline vitamin D status, differences in supplementation regimens (daily versus intermittent dosing, vitamin D_2 versus D_3), adherence issues, and methodological heterogeneity across studies. Moreover, despite improvements in BMD, evidence supporting a reduction in fracture risk remains inconclusive owing to limitations such as small sample sizes, short follow-up durations, and inconsistent fracture definitions (Bishop et al., 2014; Al-Shammari, 2025). Therefore, this study aimed to assess serum 25(OH)D, vitamin D–binding protein (DBP), and calcium levels, as well as dual-energy X-ray absorptiometry (DEXA)-derived BMD in preschool children with fractures compared them to healthy controls to evaluate the short-term outcomes of vitamin D supplementation.

2. MATERIALS AND METHODS

2.1 Study Design and Settings

This study employed a controlled cross-sectional design with an additional short-term prospective component to investigate the relationships between serum 25(OH)D, DBP, and calcium levels as well as BMD in preschool children who had fractures. The research was conducted at the Pediatric Department of Ain Shams University Hospital in Cairo, Egypt, from April to June 2023..

2.2 Study Population

The study included 90 children aged 3–5 years, allocated equally into two groups. The fracture group consisted of 45 children with fractures confirmed by radiographic imaging, while the control group included 45 healthy children matched for age and sex. Participants in the fracture group were selected from the Pediatric Orthopedic Clinic, and the controls were recruited from the General Pediatric Clinic during visits for routine health assessments, provided they had no history of fractures or chronic diseases.

The exclusion criteria encompassed any diagnosed liver or kidney disease, malabsorption syndromes, endocrine disorders that interfere with calcium or vitamin D metabolism, and a history of using corticosteroids, antiepileptic drugs, or vitamin D supplements in the 6 months preceding the study. Children with congenital bone diseases or other systemic illnesses were also excluded to limit potential confounding variables.

2.3 Clinical and Anthropometric Assessment

A detailed clinical evaluation was performed for every participant. This involved collecting data from the parents on antenatal, perinatal, and postnatal history; infant feeding practices; current dietary habits; physical activity levels; and typical sun exposure. Special attention was given to environmental and behavioral risk factors for vitamin D deficiency, including insufficient time spent outdoors, the use of concealing clothing, and suboptimal dietary intake.

Anthropometric measurements specifically height, weight, and body mass index (BMI) were obtained using standardized, calibrated equipment. BMI was computed as weight (kg) divided by the height squared (m^2), in line with standard pediatric growth assessment procedures. A comprehensive physical examination was also conducted to appraise general growth, detect any skeletal abnormalities, and check for clinical signs of rickets or vitamin D deficiency.

2.4 Biochemical Analysis

Venous blood samples (3 mL) were drawn under strict aseptic conditions. After clotting, the samples were centrifuged, and the resulting serum was aliquoted and frozen at -20 °C until analysis. Serum calcium levels (mg/dL) were measured colorimetrically using the BioVision Calcium Colorimetric Assay Kit (Abcam, UK; Cat. No. ab102505). Serum 25(OH)D concentration was quantified via enzyme-linked immunosorbent assay (ELISA) using the 25(OH) Vitamin D ELISA Kit (Abcam, UK; Cat. No. ab213966). Vitamin D status was categorized according to Endocrine Society guidelines (Bishop et al., 2014): deficiency (<50 nmol/L), insufficiency (50–75 nmol/L), and sufficiency (>75 nmol/L).

DBP levels were measured using the Human Vitamin D Binding Protein ELISA Kit (Abcam, UK; Cat. No. ab223586). All samples were assessed twice, and the average of the two measurements was used for subsequent statistical analysis to ensure accuracy. Standard internal and external quality control procedures were implemented throughout the biochemical analyses.

2.5 BMD Measurement

BMD was assessed using a Hologic Discovery A Densitometer (Hologic Inc., USA). DEXA scans were conducted at two sites, the lumbar spine (L1–L4) and the femoral neck, utilizing a pediatric software to account for variations in bone size and density related to age. A single, trained radiology technician performed all scans to reduce inter-observer variability. The results were expressed as Z-scores, where a score of 0 represents the average BMD for a child of the same age and sex. In line with the International Society for Clinical Densitometry criteria (Winzenberg et al., 2011a), a Z-score ≤ -2.0 was classified as low bone mass for chronological age.

2.6 Intervention and Follow-up

Children in the fracture group received oral vitamin D_3 supplementation at a daily dose of 600 IU, aligning with the recommendations of the American Academy of Pediatrics (Ganmaa et al., 2023). Parents were guided to maintain sufficient dietary calcium intake from sources such as milk, yogurt, and cheese, and their adherence was confirmed through parental reports at follow-up appointments. After 2 months of supplementation, children in the fracture group underwent reassessment, which included repeated measurements of serum calcium, vitamin D, and DBP, as well as a follow-up DEXA scan. The control group did not receive any supplementation and continued with their usual diet and activities.

2.7 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was verified using the Shapiro–Wilk test. Continuous variables with a normal distribution are presented as mean ± standard error (SE), and they were compared between the two groups using an independent sample t-test; a paired t-test was used for within-group comparisons pre- and post-supplementation. For non-normally distributed data, results are shown as median and interquartile range (IQR), and they were analyzed using nonparametric tests: the Wilcoxon signed-rank test for paired data and Mann–Whitney U test for independent group comparisons. The relationships between serum 25(OH)D, DBP, calcium, and BMD Z-scores were investigated using Pearson's correlation for parametric data and Spearman's rank correlation for nonparametric data. Regression analysis was performed to identify predictors of BMD and fracture risk. Univariate linear regression was conducted to assess the association between each independent variable and femoral neck BMD, followed by multivariate linear regression to determine independent predictors after adjustment for potential confounders. Similarly, univariate and multivariate logistic regression analyses were applied to evaluate factors associated with fracture risk, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Effect sizes were calculated to quantify the magnitude of differences, using Cohen's d for continuous variables and ORs for categorical outcomes. All estimates were reported with 95% CIs. Statistical significance was set at $p<0.05$.

2.8 Ethical Considerations

The study was ethically approved by the Research Ethics Committee of the Faculty of Medicine at Ain Shams University (Approval No. R68/2023). All procedures conformed to the ethical principles of the Declaration of Helsinki (2013 revision) and the institutional guidelines for research involving human subjects. Written informed consent was obtained from the parent or legal guardian of every child after a comprehensive explanation of the study's purpose, methods, potential risks, and benefits. Involvement was entirely voluntary, and guardians retained the right to withdraw their children at any stage without any effect on their clinical care. The confidentiality and anonymity of all participants were strictly upheld. All data were coded and stored securely, with access restricted to the research team. Apart from standard venipuncture, no invasive procedures were performed, and all biological samples were handled and disposed of according to the bioethical and biosafety regulations of Ain Shams University.

3. RESULTS AND DISCUSSION

3.1 Participant Demographics

No significant differences were found between both groups regarding the age ($p=0.134$) and sex distribution ($p=0.389$). Consanguinity ($p=1.000$) and feeding type ($p=0.536$) also showed no significant differences. In contrast, weight and height were significantly lower in the fracture group compared to the control group (both $p<0.001$). Additionally, delivery type demonstrated a borderline non-significant difference between the groups ($p=0.06$) (Table 1).

Table 1. Demographic and clinical characteristics of the study participants.

Variable	Fracture Group (n = 45)	Control Group (n = 45)	Test	p-value	Effect size	95% CI
Age (years)	5.24 ± 0.60	5.42 ± 0.49	T=1.514	0.134	-0.33	-0.411 to 0.055
Weight (kg)	19.22 ± 1.79	29.71 ± 4.69	T=14.01	**<0.001**	-2.96	-11.97 to -9.00
Height (cm)	113.24 ± 3.18	126.03 ± 2.26	T=21.96	**<0.001**	-4.63	-13.95 to -11.63
Sex						
Male	29 (64.4%)	25 (55.6%)	χ^2=0.741	0.389	1.45	0.62–3.38
Female	16 (35.6%)	20 (44.4%)				
Consanguinity						

Yes	11 (24.4%)	11 (24.4%)	χ^2=0	1.000	1.00	0.38–2.61
No	34 (75.6%)	34 (75.6%)				
Delivery Type						
CS	35 (77.8%)	27 (60%)	χ^2=3.138	0.06	2.33	0.93–5.85
NVD	10 (22.2%)	18 (40%)				
Feeding Type						
Breastfeeding	20 (44.4%)	15 (33.3%)	χ^2=1.246	0.536	-	-
Artificial	21 (46.7%)	26 (57.8%)				
Mixed	4 (8.9%)	4 (8.9%)				

Values are expressed as mean ± standard deviation (SD) unless otherwise specified. CS, Cesarean section; NVD, Normal vaginal delivery; p<0.05, significant; p<0.001, strongly significant.

3.2 Effect of Vitamin D Supplementation on Biochemical Parameters

A significant improvement was observed in serum 25(OH)D, calcium, and DBP levels after vitamin D supplementation (all p<0.001). Additionally, BMD showed significant improvement in the femoral neck (p<0.001). However, despite overall improvement, lumbar spine DEXA showed a reverse significant change (p<0.001), indicating a decrease in BMD that may require further evaluation or longer follow-up (Table 2).

Table 2. Biochemical parameters in the fracture group (n=45) before and after vitamin D supplementation

Parameter	Before Supplementation (Mean ± SD)	After Supplementation (Mean ± SD)	p-value	Effect size	95% CI
Serum 25(OH)D (ng/mL)	12.52 ± 4.62	20.61 ± 4.65	**<0.001**	1.66	-9.61 to -6.57
Serum Calcium (mg/dL)	8.73 ± 0.20	9.49 ± 0.36	**<0.001**	1.60	-0.904 to -0.627
Vitamin D–Binding Protein (µg/mL)	109.11 ± 9.47	122.13 ± 9.25	**<0.001**	1.16	-16.41 to -9.64
Femoral Neck DEXA (Z-score)	0.33 ± 0.11	0.62 ± 0.18	**<0.001**	1.70	-0.344 to -0.241
Lumbar Spine DEXA (Z-score)	0.83 ± 0.10	0.41 ± 0.12	**<0.001**	3.46	0.391–0.465

p<0.05, significant; p<0.001, strongly significant. DEXA, Dual-energy X-ray absorptiometry.

Strongly significant differences were observed between the fracture and control groups regarding vitamin D, DBP, and calcium levels both before and after supplementation (all p<0.001). Regarding BMD, no significant differences were observed in the femoral neck DEXA before or after supplementation (p=0.315 and p=0.364, respectively). Similarly, no significant

difference was found in the lumbar spine DEXA before supplementation (p=0.102); however, after supplementation, a significant difference was observed (p<0.001) (Table 3).

Table 3. Comparison between the fracture and control groups before and after supplementation

Parameter	Fracture Group (Mean ± SD)	Control Group (Mean ± SD)	Test Used	p-value	Effect size	95% CI
Vitamin D (Before)	12.52 ± 4.62	42.44 ± 2.06	U=2.025	**<0.001**	0.88	-31.42 to -28.42
Vitamin D (After)	20.61 ± 4.65	42.44 ± 2.06	U=2025	**<0.001**	-6.10	-23.32 to -20.34
Vitamin D–Binding Protein (Before)	109.11 ± 9.47	138.75 ± 10.40	T=14.13	**<0.001**	-2.98	-33.81 to -25.47
Vitamin D–Binding Protein (After)	122.13 ± 9.25	138.75 ± 10.40	T=8.011	**<0.001**	-1.68	-20.73 to -12.51
Calcium (Before)	8.73 ± 0.20	10.21 ± 0.18	T=36.5	**<0.001**	-7.86	-1.56 to -1.40
Calcium (After)	9.49 ± 0.36	10.21 ± 0.18	T=11.846	**<0.001**	-2.53	-0.83 to -0.61
Femoral Neck DEXA (Before)	0.33 ± 0.11	1.29 ± 3.36	U=1137	0.315	0.16	-1.95–0.03
Femoral Neck DEXA (After)	0.62 ± 0.18	1.29 ± 3.36	U=1125	0.364	-0.28	-1.98–0.64
Lumbar Spine DEXA (Before)	0.83 ± 0.10	0.78 ± 0.18	T=1.652	0.102	0.36	-0.01–0.112
Lumbar Spine DEXA (After)	0.41 ± 0.12	0.76 ± 0.17	T=11.319	**<0.001**	-2.40	-0.41 to -0.28

p<0.05, significant; p<0.001, strongly significant. DEXA, Dual-energy X-ray absorptiometry; T, independent-sample t-tests; U, Mann Whitney test.

3.3 Correlation between Biochemical Parameters and DBP

A significant positive correlation was found between DBP (before) and weight (p<0.001), height (p<0.001), male sex (p<0.001), mode of delivery by cesarean section (p=0.028), serum 25(OH)D levels (p<0.001), and calcium levels (p<0.001). In contrast, no significant correlation was found between DBP (before) and age, consanguinity, feeding type, and femoral neck or lumbar spine DEXA Z-scores (p>0.05) (Table 4).

Table 4. Correlation between biochemical parameters and DBP in the fracture group

Variables Correlated	DBP (Before)	
	(r)	**p-value**
Age	0.105	0.323
Weight	0.692**	**<0.001**

Height	0.757**	**<0.001**
Sex (Male)	0.470**	**<0.001**
Consanguinity	-0.026	0.81
Delivery (CS)	0.232*	**0.028**
Feeding type	0.071	0.504
Serum 25(OH)D (Before)	0.739	**<0.001**
Calcium (Before)	0.793**	**<0.001**
Femoral Neck DEXA Z-score (Before)	0.051	0.631
Lumbar Spine DEXA Z-score (Before)	-0.045	0.676

p<0.05, significant; p<0.001, strongly significant. DBP, vitamin D–binding protein; CS, Cesarean section; DEXA, Dual-energy X-ray absorptiometry.

3.4 BMD Predictors

Univariate linear regression analysis revealed several significant predictors of the femoral neck DEXA Z-score. Serum 25(OH)D showed a strong positive association (p<0.001), alongside the lumbar spine DEXA Z-score (p<0.001), DBP (p=0.003), weight (p=0.001), height (p=0.020), and calcium levels (p=0.040). Male sex was significantly associated with a lower femoral neck DEXA Z-score (p=0.040). Age showed a borderline significant association (p=0.050), while consanguinity, mode of delivery, and feeding type were not significant predictors (p>0.05). Overall, serum 25(OH)D and lumbar spine DEXA Z-score demonstrated the strongest predictive effect of femoral neck BMD (Table 5).

Table 5. Univariate linear regression for femoral neck DEXA Z-score

Variable	B	Standard Error	Beta	p-value
Age	0.02	0.01	0.18	0.050
Weight	0.03	0.01	0.32	**0.001**
Height	0.02	0.01	0.25	**0.020**
Sex (Male)	-0.15	0.07	-0.20	**0.040**
Consanguinity	-0.10	0.06	-0.15	0.120
Delivery (CS)	-0.06	0.05	-0.12	0.200
Feeding type	0.08	0.05	0.14	0.090
Serum 25(OH)D	0.04	0.01	0.41	**<0.001**

Calcium	0.12	0.06	0.20	**0.040**
DBP	0.01	0.003	0.28	**0.003**
Lumbar Spine DEXA Z-score	0.35	0.08	0.40	**<0.001**

p<0.05, significant; p<0.001, strongly significant. DBP, vitamin D–binding protein; CS, Cesarian section; DEXA, Dual-energy X-ray absorptiometry.

After adjusting for all included variables, multivariate linear regression analysis showed that serum 25(OH)D remained a strong independent positive predictor of the femoral neck DEXA Z-score (p<0.001), alongside lumbar spine DEXA Z-score (p<0.001). DBP was also an independent positive predictor (p=0.005), and weight remained a significant predictor, but with a weaker effect (p=0.018). In contrast, age, height, sex, consanguinity, mode of delivery, feeding type, and calcium levels were no longer significant in the adjusted model (p>0.05). Overall, serum 25(OH)D, lumbar spine DEXA Z-score, and DBP emerged as the most important independent determinants of femoral neck bone density (Table 6).

Table 6. Multivariate linear regression for femoral neck DEXA Z-score

Variable	B	Standard Error	Beta	p-value
Age	0.01	0.01	0.09	0.225
Weight	0.02	0.01	0.21	**0.018**
Height	0.01	0.01	0.11	0.178
Sex (Male)	-0.12	0.08	-0.13	0.138
Consanguinity	-0.09	0.09	-0.08	0.310
Delivery (CS)	-0.05	0.07	-0.06	0.460
Feeding type	0.06	0.05	0.10	0.240
Serum 25(OH)D	0.03	0.01	0.33	**<0.001**
Calcium	0.08	0.06	0.12	0.180
DBP	0.009	0.003	0.25	**0.005**
DEXA Lumbar Spine (Z-score)	0.28	0.07	0.31	**<0.001**

p<0.05, significant; p<0.001, strongly significant. DBP, vitamin D–binding protein; CS, Cesarian section; DEXA, Dual-energy X-ray absorptiometry.

3.5 Fracture Risk Predictors

Univariate logistic regression analysis revealed several variables that were significantly associated with fracture risk. Serum 25(OH)D showed a strong protective effect against fracture risk (p<0.001). Similarly, DBP was associated with a reduced fracture risk (p=0.010). Moreover, higher DEXA femoral neck and lumbar spine Z-scores were significantly protective (p=0.001 and p=0.002, respectively), as well as weight (p=0.010). In contrast, age, height, sex, consanguinity, mode of

delivery, feeding type, and calcium levels were not significantly associated with fracture risk (p>0.05). Overall, higher vitamin D status, DBP levels, and BMD were associated with a significantly lower risk of fractures (Table 7).

Table 7. Univariate logistic regression for fracture risk

Variable	OR	95% CI	p-value
Age	1.08	0.95–1.22	0.400
Weight	0.93	0.89–0.97	**0.010**
Height	0.97	0.94–1.01	0.200
Sex (Male)	1.50	0.85–2.60	0.150
Consanguinity	1.60	0.90–2.80	0.120
Delivery (CS)	1.20	0.80–2.10	0.300
Feeding type	0.85	0.50–1.50	0.400
Serum 25(OH)D	0.75	0.68–0.83	**<0.001**
Calcium	0.90	0.65–1.25	0.300
DBP	0.95	0.92–0.98	**0.010**
DEXA Femoral Neck	0.50	0.35–0.70	**0.001**
DEXA Lumbar Spine	0.58	0.40–0.80	**0.002**

p<0.05, significant; p<0.001, strongly significant. DBP, vitamin D–binding protein; CS, Cesarian section; DEXA, Dual-energy X-ray absorptiometry.

After adjusting for all covariates, multivariate logistic regression analysis demonstrated that several variables remained independent predictors of fracture risk. Serum 25(OH)D was a strong independent protective factor against fractures (p<0.001). DEXA femoral neck Z-score also remained a significant independent protective factor (p=0.003). In addition, weight (p=0.020) and DBP (p=0.020) were independent protective factors but with smaller effect sizes. In contrast, age, height, sex, consanguinity, mode of delivery, feeding type, and calcium levels were not significant predictors in the adjusted model (p>0.05). Overall, serum 25(OH)D, femoral neck BMD, DBP, and weight were identified as independent determinants of fracture risk, with vitamin D status and bone density showing the strongest protective effects (Table 8).

Table 8. Multivariate logistic regression for fracture risk

Variable	OR	95% CI	p-value
Age	1.05	0.90–1.21	0.520
Weight	0.95	0.91–0.99	**0.020**

Height	0.98	0.95–1.02	0.310
Sex (Male)	1.30	0.70–2.40	0.390
Consanguinity	1.40	0.75–2.60	0.280
Delivery (CS)	1.10	0.60–2.00	0.750
Feeding type	0.90	0.50–1.60	0.710
Serum 25(OH)D	0.80	0.72–0.88	**<0.001**
Calcium	0.88	0.60–1.30	0.400
DBP	0.97	0.94–0.99	**0.020**
Femoral Neck DEXA	0.55	0.35–0.80	**0.003**
Lumbar Spine DEXA	0.62	0.42–0.91	**0.015**

$p<0.05$, significant; $p<0.001$, strongly significant. DBP, vitamin D–binding protein; CS, Cesarian section; DEXA, Dual-energy X-ray absorptiometry.

3.6 Discussion

Our study findings showed no significant differences between children with fractures and healthy controls regarding age, sex distribution, consanguinity, or feeding type, indicating good comparability and suggesting that these factors did not influence fracture occurrence. Although delivery type was not a significant factor, the higher rate of Cesarean section among children with fractures may indicate a possible association that requires further investigation in larger studies. In contrast, weight and height were significantly lower in the fracture group compared to controls, which may reflect poorer nutritional status, delayed growth, or reduced bone mass acquisition. Since adequate growth is closely related to bone mineralization and skeletal strength, lower anthropometric measurements may increase susceptibility to fractures even after minor trauma. Additionally, insufficient intake of calcium, vitamin D, and other nutrients essential for bone health may contribute to this increased fracture risk.

Consistent with our findings, Varkal et al. (2022) has reported no significant differences between children with fractures and controls regarding age and sex distribution. However, a significant difference was observed in anthropometric measurements, as children in the fracture group had a higher mean BMI percentile compared to controls, indicating that increased BMI may be associated with a higher risk of fractures in children. In a meta-analysis that evaluated the effect of vitamin D supplementation on bone mineral indices in children, vitamin D had no significant effect on total body bone mineral content or BMD at the hip and forearm, with only a borderline improvement observed at the lumbar spine (Winzenberg et al., 2011b). Thus, the response of BMD to vitamin D supplementation may be site-specific and modest in magnitude. Similarly, our results showed a variable response of BMD across skeletal sites, with more pronounced changes at the lumbar spine compared to the femoral neck. Therefore, the effect of vitamin D on bone health in children is not uniform across all skeletal regions and may depend on baseline vitamin D status and site-specific differences in bone metabolism and remodeling.

Our results showed that serum 25(OH)D, calcium, and DBP levels were significantly lower in the fracture group compared to controls, which may indicate impaired bone metabolism and reduced mineral availability in children with fractures. Vitamin D plays a crucial role in calcium absorption and bone mineralization; therefore, its deficiency may lead to decreased bone strength and increased susceptibility to fractures even after minor trauma. Lower DBP levels may also reduce the transport

and bioavailability of vitamin D in circulation, further affecting skeletal health. In contrast, no significant differences were observed between the two groups regarding femoral neck and lumbar spine DEXA results, indicating that biochemical alterations in vitamin D and calcium metabolism can occur before changes are detectable in BMD, especially in preschool children where bone remodeling and growth are active. In alignment with our findings, Varkal et al. (2022) has reported significantly lower serum 25(OH) D levels in children with fractures compared to healthy controls, indicating that vitamin D deficiency may play an important role in increasing fracture susceptibility in children. This may be explained by the essential role of vitamin D in enhancing calcium absorption, maintaining bone mineralization, and supporting normal skeletal growth. Therefore, inadequate vitamin D levels can lead to reduced bone strength and increased risk of fractures, even following minor trauma. Similarly, serum 25(OH) D level assessments in children less than 2 years old with fractures revealed that a considerable proportion had suboptimal vitamin D status (Servaes et al., 2020). Although, vitamin D levels varied among participants, approximately one-third of the cohort demonstrated low vitamin D status, including both the insufficient and deficient categories. Thus, vitamin D inadequacy appears to be common in children with fractures, despite the lack of consistent severe deficiency across all cases.

Children with fractures have been reported to have lower serum 25(OH)D levels compared to healthy controls (Bouftas & DeVries, 2024), highlighting the important role of vitamin D in bone health. In the present study, the significant reduction in vitamin D, calcium, and DBP levels in the fracture group supports the association between impaired vitamin D metabolism, disturbed calcium homeostasis, and reduced bone strength. Although vitamin D deficiency is frequently linked to increased fracture risk, its effect is not always clearly reflected in BMD measurements, which may remain normal or borderline in some children. This may explain the inconsistent DEXA findings in our study despite clear biochemical differences. Overall, these results emphasize the multifactorial nature of pediatric fractures, which involve biochemical, metabolic, and growth-related factors. In contrast to our findings, an assessment of the association between vitamin D status and bone health indicators in preschool-aged children revealed no significant differences in plasma 25(OH)D and ionized calcium levels, presenting no clear association with bone health outcomes (Hazell et al., 2015). This difference was likely because the study population had adequate vitamin D levels and high calcium intake, which reduced variability and masked potential effects, unlike our cohort where deficiencies were evident.

Our results showed a significant improvement in serum 25(OH)D, calcium, and DBP levels after vitamin D supplementation, reflecting its effectiveness in resolving vitamin D deficiency and improving calcium metabolism. Since vitamin D enhances intestinal calcium absorption and supports bone mineralization, this observed biochemical improvement may have improved skeletal health and reduced fracture risk. Additionally, BMD at the femoral neck showed significant improvement after supplementation, suggesting a positive effect of vitamin D on bone strength and mineral accumulation. However, despite the overall improvement, lumbar spine DEXA findings showed a significant opposite change, indicating a decrease that may require further evaluation. This finding could be related to differences in bone remodeling rates between skeletal sites, ongoing growth-related changes in preschool children, measurement variability, or the relatively short duration of follow-up, which may have not been sufficient to detect full improvement in lumbar spine bone density.

In alignment with our findings, Winzenberg et al. (2010) reported that vitamin D supplementation resulted in modest but site-specific improvements in bone mineral outcomes in children, with the lumbar spine being the most responsive site. Furthermore, greater effects have been reported in children with vitamin D deficiency, where supplementation measurably increased bone mineral content and lumbar spine BMD, although overall changes were relatively minor. Similarly, vitamin D_3 supplementation in children demonstrated a modest but significant increase in lumbar spine BMD, particularly among those with vitamin D deficiency (Al-Shammari, 2025). This skeletal response appears to be site-specific, with the lumbar spine showing the greatest improvement, and it is more pronounced in younger children and those with low baseline vitamin D status. These findings are consistent with those of our study, where lumbar spine and femoral neck bone parameters improved following supplementation in a deficient fracture cohort. Similarly, Wu et al (2023) demonstrated that, in children and adolescents, vitamin D supplementation had a small effect on total hip BMD and no significant effects on other skeletal outcomes, indicating a modest and site-specific response of BMD to vitamin D. Consistently, in our study, we observed a differential response across skeletal sites after supplementation, with changes in femoral neck and lumbar spine Z-scores not following a uniform pattern. Therefore, vitamin D supplementation may have limited and variable effects on BMD in children, with the skeletal response depending on the anatomical site rather than showing a consistent improvement across all regions.

Our results showed highly significant differences between the fracture and control groups regarding vitamin D, DBP, and calcium levels before and after supplementation, highlighting the important role of vitamin D metabolism in bone health and fracture susceptibility in children. The low levels observed in the fracture group may reflect impaired calcium absorption and reduced bone mineralization, which contribute to weakened bones and increased fracture risk. Although supplementation improved these biochemical parameters, persistent differences between groups may indicate that children with fractures require longer treatment durations or closer nutritional monitoring to achieve optimal bone health. Regarding BMD, no significant differences were observed at the femoral neck DEXA before or after supplementation, nor in the lumbar spine DEXA before supplementation. Thus, biochemical abnormalities may appear earlier than detectable changes in BMD, particularly in growing children with active bone remodeling. However, the significant difference observed in the lumbar spine DEXA after supplementation may indicate that the lumbar spine is more sensitive to metabolic and treatment-related changes, or that regional differences in bone turnover and growth response may influence the effect of vitamin D supplementation on different skeletal sites. These findings have been confirmed in a systematic review on the association between bone density and fractures in children, where lower BMD was significantly associated with increased fracture risk in children, with a pooled analysis (SMD −0.32) indicating lower BMD in children with fractures compared to controls (Clark et al., 2006). In contrast, Zheng et al. (2021) demonstrated that no significant differences were found in serum 25(OH) D levels between children with fractures and controls, and no clear association was observed between vitamin D deficiency and fracture risk. These findings suggest that although vitamin D is crucial for bone metabolism, it may not be directly associated with fracture occurrence in all pediatric populations. Therefore, further research is warranted to confirm whether vitamin D has a causative role in fracture prevention in various pediatric populations.

The observed significant positive correlations between DBP (before) and weight, height, male sex, cesarean section delivery, serum 25(OH)D, and calcium levels indicate that vitamin D transport and availability are closely linked to overall growth status and mineral metabolism in children. Higher DBP levels in children with better anthropometric measurements may reflect improved nutritional status and hepatic protein synthesis, which are essential for vitamin D transport and stability in circulation. The association with serum 25(OH)D and calcium further supports the physiological relationship between DBP and vitamin D bioavailability, as DBP plays a key role in transporting vitamin D metabolites and maintaining calcium homeostasis.

Similarly, the strong positive correlations between serum 25(OH)D and weight, height, DBP, and calcium levels indicate that improved growth parameters are associated with improved vitamin D status and calcium metabolism, emphasizing the role of adequate nutrition and skeletal development in maintaining optimal vitamin D levels. The lack of significant correlations with age, consanguinity, feeding type, and BMD Z-scores suggests that vitamin D status and DBP are more strongly influenced by current metabolic and growth-related factors rather than baseline demographic or hereditary factors in this age group. Moreover, the borderline negative association between serum 25(OH)D and lumbar spine Z-score may indicate site-specific variability in bone response or the influence of ongoing growth and remodeling processes, which can mask early relationships between vitamin D status and bone density in young children. Consistent with our findings, Winzenberg et al. (2010) reported that vitamin D supplementation demonstrates site-specific and modest effects on bone mineral outcomes, with a more pronounced response observed in individuals with vitamin D deficiency and at the lumbar spine. However, overall effects on the whole body and peripheral bone density remain limited, highlighting the variability in skeletal responsiveness to vitamin D status.

In our study, the univariate analysis identified serum 25(OH)D, lumbar spine Z-score, DBP, weight, height, calcium, and male sex as significant predictors of femoral neck DEXA Z-score, with age showing a borderline effect, while consanguinity, mode of delivery, and feeding type were not significant. This suggests that femoral neck bone mineral status is more closely related to current biochemical and growth-related factors rather than perinatal or hereditary variables. Thus, the strong association with vitamin D status, DBP, and calcium highlights the central role of vitamin D metabolism in bone mineralization and skeletal development.

In the multivariate analysis, serum 25(OH)D, lumbar spine Z-score, and DBP remained independent predictors, indicating that these factors have a direct and sustained influence on femoral neck bone density even after adjustment for confounders. The persistence of serum 25(OH)D emphasizes its key role in calcium absorption and bone formation, while DBP reflects vitamin D transport capacity and bioavailability. Meanwhile, the persistent significance of the lumbar spine DEXA Z-score as a predictor suggests a shared systemic influence on different skeletal sites. The weaker effect of weight and the loss of

significance of other variables in the multivariate model indicate that their influence may have been indirect and largely mediated through vitamin D status and calcium metabolism rather than independently affecting on bone density. In alignment with our findings, Hazell et al. (2015) demonstrated that BMD was significantly associated with age and weight-for-age Z-score, reflecting the influence of growth-related factors on skeletal development in preschool-aged children, with higher plasma 25(OH)D concentrations (>75 nmol/L) being associated with increased BMD in the forearm and whole body. Overall, these findings indicate that both growth parameters and adequate vitamin D status are important determinants of BMD during early childhood.

In our study, the univariate analysis indicated that higher serum 25(OH)D, DBP, weight, and femoral neck and lumbar spine DEXA Z-scores were associated with a reduced risk of fractures, indicating that improved vitamin D status, BMD, and growth parameters may collectively contribute to skeletal strength and protection against fractures. In contrast, age, height, sex, consanguinity, mode of delivery, feeding type, and calcium levels were not significantly associated with fracture risk, indicating that they may have a limited direct effect in this age group or their influence may be mediated through other metabolic pathways.

In the multivariate analysis, serum 25(OH)D and femoral neck Z-score remained strong independent protective factors, emphasizing the central role of vitamin D status and BMD in maintaining bone integrity and reducing fracture susceptibility. The continued but weaker significance of DBP and weight suggests that these variables contribute indirectly to fracture protection, mainly through their relationship with vitamin D transport and overall growth status. The loss of significance of the remaining variables after adjustment indicates that their apparent effects in the univariate analysis were likely confounded by stronger biological determinants, such as vitamin D metabolism and BMD. Aligning with our findings, Varkal et al. (2022) reported that vitamin D deficiency was significantly associated with an increased risk of fractures in children, with higher BMI being associated with an increased odds of fracture occurrence.

In our study, logistic regression analysis demonstrated that lower serum vitamin D levels were associated with a higher risk of fractures, while higher BMD, DBP, and weight were identified as protective factors. Similarly, Clark et al. (2006) demonstrated that growth-related parameters play an important role in bone health and fracture risk, possibly because age and body size are closely linked to skeletal development, bone mineral acquisition, and mechanical loading on the skeleton. As children grow, increases in weight and height contribute to greater bone strength through mechanical stress and stimulation of bone formation. Hence, variations in these parameters can significantly influence BMD and may act as important confounding factors when assessing fracture risk. Therefore, interpretations of bone health outcomes in children should consider growth status alongside biochemical and metabolic factors. However, a systematic review and meta-analysis demonstrated that serum 25(OH)D levels did not significantly differ between children with fractures and control groups (Zheng et al., 2021). This may be explained by the multifactorial nature of bone strength in children and adolescents, where fracture risk is influenced not only by vitamin D status but also by factors such as bone geometry, physical activity, muscle strength, and genetic determinants. In addition, serum 25(OH)D may not fully reflect functional vitamin D activity at the bone level, and short-term variations in vitamin D status may not be sufficient to produce measurable effects on fracture occurrence. The lack of significant association may also be due to heterogeneity among studies, differences in population characteristics, and variability in defining vitamin D deficiency, potentially weakening the observed relationship between vitamin D levels and fracture risk.

Our study had some limitations. First, although the fracture group underwent a short-term prospective intervention, the baseline comparison was cross-sectional, limiting causal inferences regarding the baseline associations between vitamin D status, BMD, and fracture risk. Moreover, the 2-month follow-up period was still relatively short and may not have been sufficient to reliably characterize changes in BMD. Second, the relatively small sample size and inclusion of children from a limited age range may restrict the generalizability of the findings. Third, information regarding maternal history, infant feeding practices, current dietary habits, physical activity, sun exposure, and vitamin D supplementation were all based on parental reports; therefore, they may have been subject to recall bias. Finally, the absence of follow-up assessments in the control group limits the confirmation of whether the observed changes were attributed specifically to vitamin D supplementation rather than growth, measurement variability, or other factors. Future large-scale longitudinal studies with longer follow-up periods and objective assessments of dietary intake, sun exposure, physical activity, and Vitamin D supplementation are warranted to confirm these findings.

4. CONCLUSION

Preschool children with fractures had lower serum 25(OH)D, calcium, and DBP compared to controls, linking vitamin D deficiency to fracture risk. While baseline BMD was similar, supplementation improved biochemical markers and femoral neck BMD. Serum 25(OH)D was the strongest predictor of bone health and a protective factor against fractures, highlighting the importance of early detection and correction of deficiency. These findings support increasing clinical attention to vitamin D status in preschool children, particularly those presenting with fractures or other risk factors for poor bone health. Future longitudinal studies and larger randomized controlled trials are needed to confirm these findings and determine whether supplementation reduces subsequent fracture risk for this age group.

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AUTHOR CONTRIBUTIONS

Wafaa O. Ahmed and Eman Mohamed Elsayed: Conceptualization, Investigation, Writing—Original draft.

Hend M. Ahmed: Methodology, Laboratory Analysis.

Walaa H. Ali and Doaa Y. Hammad: Validation , Formal Analysis, Data Curation and supervision.

Aliaa El Gendy and Amira Medhat: Writing—Review & Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

The study was ethically approved by the Research Ethics Committee of the Faculty of Medicine at Ain Shams University (Approval No. R68/2023). All procedures conformed to the ethical principles of the Declaration of Helsinki (2013 revision) and the institutional guidelines for research involving human subjects. Written informed consent was obtained from the parent or legal guardian of every child after a comprehensive explanation of the study's purpose, methods, potential risks, and benefits. Involvement was entirely voluntary, and guardians retained the right to withdraw their children at any stage without any effect on their clinical care. The confidentiality and anonymity of all participants were strictly upheld. All data were coded and stored securely, with access restricted to the research team. Apart from standard venipuncture, no invasive procedures were performed, and all biological samples were handled and disposed of according to the bioethical and biosafety regulations of Ain Shams University.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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