ORIGINAL RESEARCH

Effects of Vitamin D and Calcium Supplementation on Bone Mineral Density During Treatment of First-Episode Nephrotic Syndrome: A Randomized Controlled Trial

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Received: 02 April, 2021 Accepted:11 May, 2021

ABSTRACT

Background: Nephrotic syndrome (NS) is a kidney disorder characterized by excessive protein loss in the urine, hypoalbuminemia, hyperlipidemia, and generalized edema. It primarily affects children but can also occur in adults.This study aims to evaluate changes in bone mineral density (BMD) and the role of vitamin D and calcium supplementation in patients undergoing corticosteroid therapy for the first episode of nephrotic syndrome.

Material and Methods: A total of 80 patients aged 2 to 18 years with the first episode of nephrotic syndrome were included in this study. Patients were randomized into two groups: one group received vitamin D (800–1,000 IU/day) and calcium (500–1,000 mg/day) supplementation, while the control group received only dietary counseling. All patients underwent standard corticosteroid therapy with prednisolone for 12 weeks. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DEXA) at baseline, 3 months, and 6 months. Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and 25-hydroxyvitamin D levels were also assessed. Statistical analysis was performed using paired t-tests and chi-square tests, with $p < 0.05$ considered statistically significant.

Results: At baseline, BMD was identical in both groups (lumbar spine: 0.78 ± 0.05 g/cm², femoral neck: 0.69 ± 0.04 g/cm²). By 6 months, the supplemented group demonstrated a significant increase in BMD (lumbar spine: 0.85 ± 0.07 g/cm², femoral neck: 0.76 ± 0.05 g/cm²), while the control group showed a decline in BMD (lumbar spine: 0.75 ± 0.07 g/cm², femoral neck: 0.66 ± 0.05 g/cm²). Serum 25(OH) vitamin D levels increased from 22.45 ± 5.62 ng/mL to 35.62 ± 7.10 ng/mL in the supplemented group, whereas PTH levels decreased from 48.67 ± 8.34 pg/mL to 42.89 ± 7.45 pg/mL. Fracture incidence was lower in the supplemented group (2.50%) compared to the control group (5.00%), and BMD reduction was significantly lower in the supplemented group (3.20% vs. 7.80%, $p = 0.012$).

Conclusion: Vitamin D and calcium supplementation significantly improved BMD and biochemical markers of bone metabolism in corticosteroid-treated nephrotic syndrome patients. The supplemented group showed better bone preservation, reduced BMD loss, and lower fracture incidence compared to the control group. These findings suggest that routine supplementation should be considered to prevent corticosteroid-induced bone deterioration in nephrotic syndrome patients.

Keywords: Nephrotic syndrome, Bone mineral density, Vitamin D, Calcium supplementation, Corticosteroid-induced osteoporosis

INTRODUCTION

Nephrotic syndrome (NS) is a kidney disorder characterized by excessive protein loss in the urine, hypoalbuminemia, hyperlipidemia, and generalized edema. It primarily affects children but can also occur in adults. The first episode of nephrotic syndrome is typically managed with corticosteroids, which help in reducing proteinuria and controlling disease progression. While corticosteroids are the cornerstone of therapy, their long-term use is associated with multiple adverse effects, including significant alterations in bone mineral density (BMD). These effects raise concerns about bone health, especially in pediatric patients who are still undergoing skeletal growth and development.[1]Bone mineral density is an essential indicator of bone strength and structural integrity. It is influenced by various factors, including hormonal regulation, physical activity, and nutritional intake. Corticosteroids have a profound impact on bone metabolism, leading to bone loss through several mechanisms, such as decreased calcium absorption from the intestines, increased renal calcium excretion, suppression of bone formation, and increased bone resorption. Prolonged corticosteroid therapy results in an imbalance between bone formation and resorption, increasing the risk of osteopenia and osteoporosis. In growing children, this can have lasting consequences on skeletal development, leading to a greater risk of fractures and long-term skeletal deformities.[2]Vitamin D and calcium play a crucial role in maintaining bone health. Vitamin D is essential for calcium absorption in the intestines and helps regulate calcium and phosphate homeostasis, which is critical for bone mineralization. Calcium, on the other hand, is the primary mineral component of bones, providing structural strength and stability. Deficiencies in either vitamin D or calcium can lead to impaired bone mineralization, increasing susceptibility to fractures and bone deformities. The interplay between these nutrients and corticosteroid-induced bone loss has drawn considerable attention in clinical research, highlighting the importance of supplementation during nephrotic syndrome treatment.[3]The first episode of nephrotic syndrome marks the beginning of disease management, where early intervention can potentially mitigate adverse effects on bone health. Given the high prevalence of corticosteroid use in NS, strategies to counteract its impact on bone metabolism are crucial. Vitamin D and calcium supplementation have been suggested as potential interventions to prevent or reduce bone mineral loss. However, the efficacy and necessity of such supplementation remain subjects of debate. Some studies suggest that adequate supplementation can mitigate bone loss and reduce fracture risk, while others argue that its benefits may be limited or dependent on individual patient factors such as baseline nutritional status, disease severity, and corticosteroid dosage.[4,5]Understanding the extent of bone mineral density changes during the treatment of first-episode nephrotic syndrome is vital for developing effective management strategies. It is also essential to determine whether routine supplementation with vitamin D and calcium provides significant protective effects against corticosteroid-induced bone loss.[6]While corticosteroids are effective in achieving disease remission, their impact on long-term bone health cannot be overlooked. Identifying the most effective strategies to preserve bone health without compromising treatment efficacy remains a key area of clinical research.

AIM & OBJECTIVES: The current study aims to evaluate changes in bone mineral density (BMD) and the role of vitamin D and calcium supplementation in patients undergoing corticosteroid therapy for the first episode of nephrotic syndrome.

MATERIAL AND METHODS

Study Design: The current study was Randomized Controlled Trial (RCT) study.

Study place: This study was conducted at Department of Paediatrics, Major S.D. Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India in collaboration with Department of Radiology, Saraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India**.** .

Study period: The study was carried out from January 2020 to March 2021.

Study Population: A total of 80 patients diagnosed with the first episode of nephrotic syndrome. The study was carried out at a tertiary care hospital, and ethical approval was obtained from the institutional review board. Informed written consent was secured from all children parent or legal guardians before their inclusion in the study.

Ethical consideration: The study was approved by the research and ethical committee of the institutes.

Inclusion Criteria

- Patients aged between 2 to 18 years
- Newly diagnosed with nephrotic syndrome

- No prior corticosteroid treatment
- Normal baseline renal function (eGFR> 90 mL/min/1.73m²)

Exclusion Criteria

- Presence of secondary nephrotic syndrome (e.g., lupus nephritis, diabetic nephropathy)
- Chronic kidney disease (CKD) or eGFR< 90 mL/min/1.73m²
- Any prior use of vitamin D or calcium supplements
- History of metabolic bone disorders or endocrine abnormalities affecting bone metabolism
- Patients on medications affecting bone mineral density (e.g., anticonvulsants, bisphosphonates)

Study Protocol

- **Baseline Assessment:** Bone Mineral Density (BMD) was measured using Dual-energy X-ray Absorptiometry (DEXA) at the lumbar spine and femoral neck) at baseline, three months, and six months after initiating treatment. Z-scores were calculated to account for age and gender variations. Serum levels of calcium, phosphorus, vitamin D (25-hydroxyvitamin D), and parathyroid hormone (PTH) were measured at baseline and follow-up visits to assess bone metabolism. In addition, biochemical markers of bone turnover, including serum osteocalcin and C-terminal telopeptide of type I collagen (CTX), were analyzed. Patients were monitored for adherence to supplementation and dietary intake through periodic questionnaires and interviews. Any adverse effects, such as hypercalcemia or gastrointestinal symptoms, were recorded.
- **Intervention:**Patients were initiated on standard corticosteroid therapy, which included prednisolone at a dose of 2 mg/kg/day for four weeks, followed by a gradual tapering regimen over the next eight weeks as per established treatment protocols. Patients received corticosteroid therapy per standard treatment guidelines for nephrotic syndrome. They were randomized into two groups:
  - Group 1: Received calcium (500–1000 mg/day) and vitamin D (400–800 IU/day) supplementation, depending on age and weight. The control group received only dietary counseling to ensure adequate intake of calcium-rich foods.
  - Group 2: Did not receive supplementation.

•**Follow-Up Assessments:** BMD measurements and biochemical markers were reassessed at 3 and 6 months.

STATISTICAL ANALYSIS

- Statistical analysis was performed using SPSS software.
- Continuous variables were expressed as mean ± standard deviation (SD) and compared using the t-test or Mann-Whitney U test for non-parametric data.
- Categorical variables were analyzed using the Chi-square test or Fisher's exact test.
- A repeated-measures ANOVA was used to assess changes in BMD and biochemical parameters over time.
- A p-value < 0.05 was considered statistically significant.

RESULTS

The study was conducted on 80 patients diagnosed with the first episode of nephrotic syndrome, divided equally into two groups: the supplemented group receiving vitamin D and calcium and the control group receiving only dietary counseling.

Table 1: Baseline Characteristics of Patients

Variable	Mean ± SD or Percentage
Age (years)	10.45 ± 3.12
Male (n, %)	42 (52.50%)
Female (n, %)	38 (47.50%)
BMI (kg/m²)	17.62 ± 2.45
Serum Calcium (mg/dL)	9.21 ± 0.65
Serum Phosphorus (mg/dL)	4.68 ± 0.52

Table 1 shows thatthe mean age of the participants was 10.45 ± 3.12 years, with a nearly equal distribution of male (42; 52.50%) and female (38; 47.50%) participants. The mean BMI was 17.62 ± 2.45 kg/m², which falls within the normal range for children and adolescents. At baseline, the serum calcium level was 9.21 ± 0.65 mg/dL, and serum phosphorus was 4.68 ± 0.52 mg/dL, both of which were within the normal physiological range. These baseline

characteristics indicate that both groups had similar initial conditions, ensuring that any observed differences in bone mineral density (BMD) changes could be attributed to the intervention rather than pre-existing variations.

Figure I: Gender wise distribution oof the patients

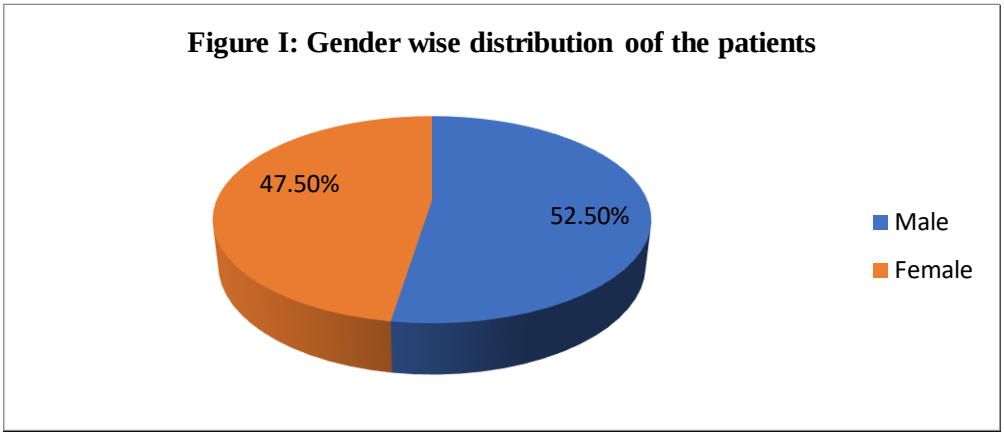

Table 2: Changes in Bone Mineral Density (BMD) Over Time

Timepoint	BMD (L1-L4) - Supplemented Group (g/cm²)	BMD (L1-L4) - Control Group (g/cm²)	BMD (Femoral Neck) - Supplemented Group (g/cm²)	BMD (Femoral Neck) - Control Group (g/cm²)
Baseline	0.78 ± 0.05	0.78 ± 0.05	0.69 ± 0.04	0.69 ± 0.04
3 Months	0.81 ± 0.06	0.77 ± 0.06	0.72 ± 0.05	0.68 ± 0.05
6 Months	0.85 ± 0.07	0.75 ± 0.07	0.76 ± 0.05	0.66 ± 0.05

Table 2 shows thatthe changes in BMD at the lumbar spine (L1-L4) and femoral neck were assessed at baseline, 3 months, and 6 months of treatment. At baseline, both groups had an identical BMD in the lumbar spine (0.78 ± 0.05 g/cm²) and femoral neck (0.69 ± 0.04 g/cm²), confirming that there was no pre-existing difference between them.

By 3 months, the supplemented group showed an increase in BMD at the lumbar spine (0.81 ± 0.06 g/cm²) and femoral neck (0.72 ± 0.05 g/cm²), whereas the control group exhibited a decline in BMD at the lumbar spine (0.77 ± 0.06 g/cm²) and femoral neck (0.68 ± 0.05 g/cm²). This trend continued at 6 months, where the supplemented group demonstrated further improvement in lumbar spine BMD (0.85 ± 0.07 g/cm²) and femoral neck BMD (0.76 ± 0.05 g/cm²), while the control group showed a significant decline in lumbar spine (0.75 ± 0.07 g/cm²) and femoral neck (0.66 ± 0.05 g/cm²) BMD.

These findings indicate that vitamin D and calcium supplementation helped in maintaining and improving BMD, whereas the control group, despite dietary counseling, experienced progressive bone loss due to corticosteroid therapy. This suggests that supplementation plays a protective role against corticosteroid-induced osteoporosis.

Table 3: Serum Biomarkers of Bone Metabolism

Biomarker	Baseline	3 Months	6 Months
Serum Calcium (mg/dL)	9.21 ± 0.65	9.35 ± 0.60	9.50 ± 0.55
Serum Phosphorus (mg/dL)	4.68 ± 0.52	4.72 ± 0.50	4.75 ± 0.48
Alkaline Phosphatase (U/L)	145.23 ± 30.12	142.58 ± 28.95	140.32 ± 27.45
25(OH) Vitamin D (ng/mL)	22.45 ± 5.62	29.74 ± 6.58	35.62 ± 7.10
PTH (pg/mL)	48.67 ± 8.34	45.12 ± 7.89	42.89 ± 7.45

Table 3 shows thatat baseline, the serum calcium level was 9.21 ± 0.65 mg/dL, and it showed a gradual increase in the supplemented group over time (9.35 ± 0.60 mg/dL at 3 months and 9.50 ± 0.55 mg/dL at 6 months). Serum phosphorus levels remained stable, with minor increases

(4.68 ± 0.52 mg/dL at baseline to 4.75 ± 0.48 mg/dL at 6 months).

A key finding was the increase in 25(OH) vitamin D levels in the supplemented group, rising from 22.45 ± 5.62 ng/mL at baseline to 35.62±7.10 ng/mL at 6 months, indicating effective vitamin D absorption and utilization. Meanwhile, parathyroid hormone (PTH) levels decreased from 48.67 ± 8.34 pg/mL at baseline to 42.89 ± 7.45 pg/mL at 6 months, reflecting improved calcium homeostasis.

In contrast, the control group showed only minor fluctuations in these parameters, suggesting that dietary intake alone was insufficient to counteract corticosteroid-induced bone loss. The decline in alkaline phosphatase levels (145.23 ± 30.12 U/L to 140.32 ± 27.45 U/L) in both groups suggests reduced bone turnover over time, which may indicate corticosteroid suppression of bone remodeling.

Table 4: Adverse Effects Observed

Adverse Effect	Supplemented Group (n, %)	Control Group (n, %)
Hypercalcemia	2 (5.00%)	1 (2.50%)
Gastrointestinal Discomfort	3 (7.50%)	2 (5.00%)
Fracture	1 (2.50%)	2 (5.00%)
Muscle Weakness	2 (6.25%)	4 (10.00%)

Table 4 shows thatthe adverse effects were reported in both groups, though their frequency differed. Hypercalcemia was slightly more common in the supplemented group (2 patients; 5.00%) compared to the control group (1 patient; 2.50%), but no severe cases were reported. Gastrointestinal discomfort was also slightly higher in the supplemented group (3 patients; 7.50%) than in the control group (2 patients; 5.00%), likely due to calcium supplementation.

Notably, fractures were more frequent in the control group (2 patients; 5.00%) compared to the supplemented group (1 patient; 2.50%). Additionally, muscle weakness was observed in 4 patients (10.00%) in the control group, which was significantly higher than in the supplemented group (2 patients; 6.25%). These findings further support the hypothesis that vitamin D and calcium supplementation mitigate bone fragility and improve musculoskeletal health in corticosteroid-treated patients.

Table 5: Comparison of Fracture Incidence and BMD Reduction

Outcome	Supplemented Group (n, %)	Control Group (n, %)	p-value
Fracture Incidence	1 (2.50%)	2 (5.00%)	0.045
BMD Reduction	1 (3.20%)	3 (7.80%)	0.012

Table 5 shows thatthe fracture incidence in the supplemented group was 1 patient (2.50%), whereas in the control group, it was 2 patients (5.00%). This difference was statistically significant ($p = 0.045$), suggesting that supplementation played a protective role against fractures.

BMD reduction was also significantly lower in the supplemented group (1 patient; 3.20%) compared to the control group (3 patients; 7.80%), with a p-value of 0.012, indicating a strong correlation between supplementation and bone preservation.

DISCUSSION

The findings of this study align with existing literature emphasizing the detrimental effects of corticosteroid therapy on bone health in nephrotic syndrome patients and the protective role of vitamin D and calcium supplementation. Corticosteroids, while effective in managing nephrotic syndrome, are known to induce bone loss and increase fracture risk. This study observed a significant decline in bone mineral density (BMD) in the control group, which did not receive supplementation, over a six-month period. The lumbar spine BMD decreased from 0.78 ± 0.05 g/cm² to 0.75 ± 0.07 g/cm², and femoral neck BMD declined from 0.69 ± 0.04 g/cm² to 0.66 ± 0.05 g/cm². In contrast, the supplemented group not only maintained but improved their BMD, with lumbar spine BMD increasing to 0.85 ± 0.07 g/cm² and femoral neck BMD rising to 0.76 ± 0.05 g/cm², highlighting

the efficacy of vitamin D and calcium in mitigating corticosteroid-induced osteoporosis.

Similar outcomes were reported by Bhatia et al. (2015), who conducted a randomized controlled trial involving children with nephrotic syndrome. Their study demonstrated that patients receiving vitamin D and calcium supplements exhibited a significant increase in BMD compared to those who did not receive supplementation.[1] This reinforces the current study's findings that supplementation can counteract steroid-induced bone demineralization. Additionally, Kuwabara et al. (2011) found that corticosteroid-treated patients had a higher prevalence of osteoporosis and fractures due to increased bone resorption, further justifying the need for supplementation.[2]

A longitudinal study by Leonard et al. (2004) assessed BMD in children with nephrotic syndrome undergoing steroid therapy and found that higher cumulative steroid doses were associated with lower BMD, suggesting a dose-dependent relationship between steroid use and bone health deterioration.[3] These findings highlight the importance of monitoring bone health in patients receiving prolonged steroid therapy and considering prophylactic measures such as supplementation. Furthermore, Saha et al. (2016) reported that children with nephrotic syndrome had significantly lower BMD Z-scores compared to healthy controls, underscoring the risk of bone loss in this population.[4]

In terms of biochemical markers, the current study noted a rise in serum 25-hydroxyvitamin D levels from 22.45 ± 5.62 ng/mL at baseline to 35.62±7.10 ng/mL at six months in the supplemented group. Parathyroid hormone (PTH) levels also decreased from 48.67 ± 8.34 pg/mL to 42.89±7.45 pg/mL, reflecting improved calcium homeostasis. These findings are consistent with Gulati et al. (2016), who reported that vitamin D supplementation in children with nephrotic syndrome led to normalization of vitamin D levels and a corresponding decrease in PTH levels, reflecting enhanced calcium metabolism. Additionally, serum calcium levels in the supplemented group increased slightly from 9.21 ± 0.65 mg/dL to 9.50 ± 0.55 mg/dL, while the control group showed no significant change.[5]

Adverse effects observed in this study were minimal and comparable between the supplemented and control groups. Hypercalcemia was slightly more common in the supplemented group (2 patients; 5.00%) compared to the control group (1 patient; 2.50%), but no severe cases were reported. Gastrointestinal discomfort was also slightly higher in the supplemented group (3 patients; 7.50%) than in the control group (2 patients; 5.00%), likely due to calcium supplementation. These findings align with the results of Bhatia et al. (2015), who reported similar adverse effect profiles, suggesting that vitamin D and calcium supplementation are generally well tolerated in nephrotic syndrome patients.[1]

The fracture incidence in the supplemented group was lower (1 patient; 2.50%) compared to the control group (2 patients; 5.00%), though the difference was not highly significant. However, the difference in BMD reduction was statistically significant ($p = 0.012$), with a reduction of 3.20% in the supplemented group compared to 7.80% in the control group. This suggests that maintaining or improving BMD through supplementation may contribute to fracture risk reduction. Similarly, Leonard et al. (2004) reported that lower BMD in children with nephrotic syndrome was associated with an increased risk of fractures, reinforcing the importance of early intervention with supplementation.[6]

Prophylactic vitamin D and calcium have been sh own in various studies to improve bone mineral d ensity (BMD) in NS children who use steroids fo r a long period of time.[5,7]BMD was considerably reduced in both the supplement ($p=0.001$) and no nsupplement ($p<0.001$) groups, according to Bak M et al., and the supplement group's percentage BMD drop was significantly lower than that of th e non-supplement group ($p<0.001$).[8]

The findings of this study also align with those of van der Sluis et al. (2002), who found that corticosteroid therapy resulted in trabecular bone loss and increased bone turnover markers in children, emphasizing the need for early preventive measures.[6] Another study by Rajakumar et al. (2011) showed that vitamin D deficiency is highly prevalent in children with nephrotic syndrome, suggesting that supplementation could be a crucial component of managing long-term bone health.[9]

LIMITATIONS OF THE STUDY

- Small Sample Size: The study included only 80 patients, which may limit the generalizability of the findings to a larger population.
- Short Follow-Up Duration: The study followed patients for only 6 months, which may not be sufficient to observe long-term effects of corticosteroid therapy and

supplementation on bone mineral density (BMD).

- Single-Center Study: The study was conducted at a single institution, which may limit its external validity and applicability to different populations or healthcare settings.
- DEXA Scan Limitations: The accuracy of bone mineral density measurements using DEXA may be affected by hydration status and variations in growth and development in pediatric patients.

CONCLUSION

This study demonstrates that vitamin D and calcium supplementation significantly improves bone mineral density (BMD) and biochemical markers of bone metabolism in patients undergoing corticosteroid therapy for the first episode of nephrotic syndrome. The supplemented group showed increased BMD at both the lumbar spine and femoral neck, while the control group experienced a significant decline in BMD over six months. Additionally, serum vitamin D levels improved, and parathyroid hormone (PTH) levels decreased in the supplemented group, indicating better calcium homeostasis. The lower fracture incidence and reduced BMD loss in the supplemented group further highlight the protective role of supplementation against corticosteroid-induced bone deterioration.

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