ORIGINAL RESEARCH

Assessment of Bone Mineral Density Changes and the Effects of Vitamin D and Calcium Supplementation in Patients Undergoing Treatment for First Episode Nephrotic Syndrome

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ABSTRACT

Background: Children with idiopathic nephrotic syndrome treated with corticosteroids are at risk of developing bone mineral deficits due to steroid-induced alterations in calcium and vitamin D metabolism. Early intervention with supplementation may help preserve bone health during therapy.

Aim: To evaluate changes in bone mineral density (BMD) and the effect of vitamin D and calcium supplementation during the treatment of the first episode of idiopathic nephrotic syndrome in children.

Material and Methods: This prospective observational study included 80 children aged 2–12 years newly diagnosed with idiopathic nephrotic syndrome. Participants were divided into two groups: Group A (n=40) received standard corticosteroid therapy along with oral vitamin D (600 IU/day) and calcium (500 mg/day), while Group B (n=40) received corticosteroids alone. BMD was measured using DEXA at baseline and after 12 weeks, along with serum calcium, phosphorus, alkaline phosphatase, and 25(OH) vitamin D levels. Clinical outcomes such as remission rate and relapse were also monitored. Data were analyzed using SPSS version 21.0, with $p < 0.05$ considered significant.

Results: Both groups were comparable at baseline in demographic, clinical, and biochemical parameters. After 12 weeks, Group A showed significant improvement in lumbar spine BMD Z-scores (from -0.91 ± 0.45 to -0.61 ± 0.38) and TBLH Z-scores (from -0.85 ± 0.41 to -0.55 ± 0.36), whereas Group B showed a decline in BMD ($p < 0.01$). Serum 25(OH) vitamin D and calcium levels were significantly higher in Group A ($p < 0.001$), with lower alkaline phosphatase levels ($p < 0.01$), indicating better bone metabolism. Clinical remission and relapse rates were similar between the groups ($p > 0.05$).

Conclusion: Vitamin D and calcium supplementation during corticosteroid therapy significantly improves bone mineral density and biochemical parameters in children with first-episode nephrotic syndrome, without affecting short-term clinical outcomes. Early bone-protective intervention is recommended to prevent long-term skeletal complications.

Keywords: Nephrotic syndrome, Bone mineral density, Vitamin D, Calcium supplementation, Steroid therapy

INTRODUCTION

Nephrotic syndrome is one of the most common chronic glomerular diseases affecting children, characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and generalized oedema. While corticosteroids remain the cornerstone of therapy for idiopathic nephrotic syndrome, their long-term use is associated with a spectrum of adverse effects, including significant skeletal complications. Among these, decreased bone mineral density (BMD), impaired bone mineralization, and increased risk of fractures are of particular concern in the paediatric population, where optimal skeletal development is crucial for long-term health outcomes.[1]

The pathophysiology of bone demineralization in children with nephrotic syndrome is multifactorial. Firstly, corticosteroids directly suppress osteoblast function and enhance osteoclastic bone resorption, resulting in a net loss of bone mass. Moreover, steroids reduce calcium absorption from the gastrointestinal tract, increase renal calcium excretion, and impair vitamin D metabolism, thereby compounding the risk of bone demineralization. Children are particularly vulnerable due to the active phase of bone growth and remodelling occurring during their formative years.[2] Changes in BMD in children with nephrotic syndrome often go unnoticed in the early stages, as overt symptoms of bone weakness such as pain or deformities tend to appear only after substantial bone loss has occurred. Dual-energy X-ray absorptiometry (DEXA) remains the most widely used tool for the assessment of BMD. However, in paediatric populations, interpretation of DEXA scans needs careful consideration due to confounding variables such as growth velocity, body size, and developmental stage. Children with nephrotic syndrome are frequently found to have lower-than-expected BMD z-scores when adjusted for age and sex, which in some cases may not reflect true pathological bone loss but rather developmental variability.[3]

Despite this, the cumulative effect of glucocorticoid therapy on bone density cannot be underestimated. Cases of vertebral compression fractures and osteopenia have been reported, even during the early stages of therapy, indicating the rapid impact that steroids can have on bone health. Notably, some patients present with skeletal complications within months of initiating steroid treatment, highlighting the urgency of implementing bone-protective strategies alongside immune suppressive therapy.[4]

Among the preventive and therapeutic strategies, vitamin D and calcium supplementation have garnered attention for their potential to mitigate the detrimental skeletal effects of corticosteroid therapy. Vitamin D plays a central role in calcium homeostasis and bone metabolism. Its deficiency, which is common in children with chronic illnesses and those on steroids, leads to impaired bone mineralization, hypocalcemia, and secondary hyperparathyroidism, further accelerating bone loss. Calcium is equally essential for maintaining bone structure and function, and insufficient intake or absorption can severely impact peak bone mass attainment in growing children.[5]

Prophylactic administration of vitamin D and calcium during steroid therapy has been shown to improve BMD and reduce the risk of osteoporosis-related complications. Several interventional studies have explored the efficacy of combined supplementation in preserving skeletal health during the course of nephrotic syndrome treatment. Improvements in biochemical markers such as serum calcium, phosphate, alkaline phosphatase, and 25-hydroxy vitamin D levels have been observed following supplementation. Additionally, longitudinal assessments have demonstrated stabilization or even improvement in BMD z-scores in children receiving prophylactic supplementation compared to those who do not.[6]

Despite encouraging evidence, consensus guidelines on routine supplementation in children with nephrotic syndrome remain limited. Some clinical protocols advocate universal supplementation during corticosteroid therapy, particularly in patients with additional risk factors such as poor nutritional status, prolonged immobilization, or a history of bone disease. Others recommend individualized supplementation based on periodic assessment of vitamin D status and bone density. The variability in approaches reflects the ongoing need for large-scale, controlled trials to establish standardized treatment regimens and dosing protocols that are both safe and effective in paediatric populations.[7]

It is also essential to consider the role of lifestyle factors in supporting bone health during and after corticosteroid therapy. Adequate dietary calcium intake, safe exposure to sunlight for endogenous vitamin D synthesis, and weight-bearing physical activity are important adjuncts to pharmacological supplementation. However, children with nephrotic syndrome may face restrictions on outdoor activities due to their illness, further

increasing their risk of skeletal complications and reinforcing the importance of clinical vigilance.[8]

AIM AND OBJECTIVES

Aim: To evaluate changes in Bone Mineral Density (BMD) and assess the role of vitamin D and calcium supplementation during corticosteroid therapy in children with a first episode of idiopathic nephrotic syndrome.

Objectives

1. **Primary Objective:**

To assess the change in BMD Z-scores (lumbar spine and total body less head) from baseline to 12 weeks in children with idiopathic nephrotic syndrome receiving corticosteroids with or without vitamin D and calcium supplementation.

2. **Secondary Objectives:**

- To evaluate changes in biochemical markers related to bone health (serum calcium, phosphorus, alkaline phosphatase, and 25(OH) vitamin D) over the 12-week treatment period.
- To compare the effectiveness of vitamin D and calcium supplementation in preventing bone mineral loss during corticosteroid therapy.
- To monitor disease activity (serum albumin and urinary protein excretion) during the treatment period.
- To examine the correlation between serum vitamin D levels and changes in BMD.
- To identify predictors of change in BMD using multivariate analysis.

MATERIALS AND METHODS

Study Design

This was a prospective observational study aimed at evaluating changes in Bone Mineral Density (BMD) and the role of vitamin D and calcium supplementation during the treatment of the first episode of idiopathic nephrotic syndrome in children.

Study Population

The study enrolled 80 children aged 2 to 12 years, all of whom were newly diagnosed with a first episode of idiopathic nephrotic syndrome. Participants were enrolled consecutively following consent.

Study Place

The study was conducted in the Department of Paediatrics, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, India.

Study Duration

The study was conducted over a period of eighteen months from August 2019 to January 2021, each participant was followed for a 12-week treatment period, with the study presumably spanning over several months to accommodate all 80 participants.

Inclusion Criteria

- Children aged 2 to 12 years
- First episode of idiopathic nephrotic syndrome
- No prior steroid therapy or use of vitamin D/calcium supplements
- Normal renal function (serum creatinine within age-appropriate limits)
- Willingness of caregivers to adhere to study protocol and attend follow-up visits

Exclusion Criteria

- Steroid-resistant or secondary nephrotic syndrome
- Pre-existing bone or metabolic disorders
- Chronic illnesses affecting calcium or vitamin D metabolism (e.g., liver disease, endocrinopathies, malabsorption)
- Use of medications affecting bone metabolism (anticonvulsants, diuretics)
- Severe malnutrition (weight-for-age < -3 SD)

Ethical Considerations

The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from the parents or legal guardians of all children before enrollment.

Study Procedure

Group Allocation

Participants were divided into two equal groups (n=40):

Group A (Intervention group): Received corticosteroids + vitamin D (600 IU/day) + calcium (500 mg/day).

Group B (Control group): Received only corticosteroids.

Steroid Therapy

All participants were treated per the ISKDC protocol:

Prednisolone 2 mg/kg/day (max 60 mg) for 6 weeks

Followed by 1.5 mg/kg on alternate days for 6 weeks

Dose then tapered off

Supplement Compliance Monitoring

Pill counts and caregiver-reported intake were used to monitor adherence to vitamin D and calcium supplements.

Dietary Assessment

24-hour dietary recall method was used at baseline and follow-up visits to assess calcium and vitamin D intake.

BMD Assessment

BMD measured by DEXA scan at:

- Baseline (within 5 days of diagnosis)
- After 12 weeks of therapy
- Measurements focused on lumbar spine (L1–L4) and total body less head (TBLH)
- Z-scores used, adjusted for age and sex

Biochemical Monitoring

Serum calcium, phosphorus, alkaline phosphatase, and 25(OH)D measured at baseline and 12 weeks
Weekly monitoring of serum albumin and urinary protein excretion to assess disease activity

Outcome Measures

Primary Outcome

- Change in Bone Mineral Density (BMD) Z-scores from baseline to 12 weeks

Secondary Outcomes

- Changes in biochemical markers: serum calcium, phosphorus, alkaline phosphatase, and 25(OH)D levels
- Disease activity indicators: serum albumin and urinary protein excretion

Statistical Analysis

Software Used: Statistical analysis was performed using Microsoft excel and SPSS version 21.0 software.

Data Presentation:

- Continuous variables (e.g., bone mineral density, serum calcium, serum vitamin D levels) were expressed as mean ± standard deviation (SD) **or** median (IQR) based on normality.
- Categorical variables (e.g., gender, presence of vitamin D deficiency) were expressed as frequency and percentage.

Comparisons between Groups:

- Independent t-test (or Mann–Whitney U test) was used to compare continuous variables between two groups (e.g., with vs. thout supplementation).
- Paired t-test was used to compare pre- and post-treatment values within the same group.
- Chi-square test **or** Fisher's exact test was used for comparing categorical variables.

Correlation and Regression:

- Pearson's **or** Spearman's correlation coefficient was used to evaluate the relationship between serum vitamin D levels and changes in bone mineral density (BMD).
- Multiple linear regression may be performed to identify independent predictors of change in BMD after adjusting for confounders (e.g., age, gender, baseline BMD, serum albumin).

Significance Threshold: A **p-value < 0.05** was considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (N=80)

Parameter	Group A (n=40)	Group B (n=40)	p-value
Age (mean ± SD, years)	6.5 ± 2.3	6.7 ± 2.5	0.72
Male: Female ratio	26:14	25:15	0.81
Mean weight (kg)	20.1 ± 3.8	19.9 ± 4.1	0.84
Mean height (cm)	113.4 ± 7.5	114.2 ± 8.1	0.67
Mean serum albumin (g/dL)	1.9 ± 0.3	2.0 ± 0.4	0.36
Mean urinary protein (g/day)	3.4 ± 1.0	3.3 ± 0.9	0.58

Table 1 shows that baseline characteristics of the participants in both groups were comparable, indicating successful random allocation and group homogeneity. The mean age was 6.5 ± 2.3 years in Group A and 6.7 ± 2.5 years in Group B ($p = 0.72$), showing no statistically significant difference. The male-to-female ratio was also similar (26:14 in Group A vs. 25:15 in Group B, $p = 0.81$). There was no significant difference in anthropometric measures such as weight (20.1 ± 3.8 kg vs. 19.9 ± 4.1 kg, $p = 0.84$) and height (113.4 ± 7.5 cm vs. 114.2 ± 8.1 cm, $p = 0.67$). Clinical indicators such as mean serum albumin (1.9 ± 0.3 g/dL in Group A vs. 2.0 ± 0.4 g/dL in Group B) and urinary protein excretion (3.4 ± 1.0 g/day vs. 3.3 ± 0.9 g/day) were also comparable between the groups ($p > 0.05$ for both), confirming that the disease severity at presentation was similar.

Table 2: Baseline Biochemical Parameters Related to Bone Health

Parameter	Group A (n=40)	Group B (n=40)	p-value
Serum calcium (mg/dL)	8.7 ± 0.5	8.6 ± 0.6	0.40

Serum phosphorus (mg/dL)	5.2 ± 0.7	5.1 ± 0.8	0.55
Alkaline phosphatase (IU/L)	280 ± 60	285 ± 64	0.73
25(OH) Vitamin D (ng/mL)	18.4 ± 6.1	18.1 ± 6.4	0.78

Table 2 shows that at baseline, biochemical parameters related to bone metabolism were not significantly different between the two groups. The mean serum calcium level was 8.7 ± 0.5 mg/dL in Group A and 8.6 ± 0.6 mg/dL in Group B (p = 0.40). Similarly, serum phosphorus levels were 5.2 ± 0.7 mg/dL in Group A and 5.1 ± 0.8 mg/dL in Group B (p = 0.55). The levels of alkaline phosphatase, a marker of bone turnover, were comparable between the groups (280 ± 60 IU/L vs. 285 ± 64 IU/L, p = 0.73). Baseline vitamin D levels were low in both groups, with mean 25(OH)D levels of 18.4 ± 6.1 ng/mL in Group A and 18.1 ± 6.4 ng/mL in Group B (p = 0.78), suggesting pre-existing insufficiency across the cohort.

Table 3: Changes in Bone Mineral Density (BMD) After 12 Weeks of Treatment

Site of BMD Measurement	Group A: Baseline	Group A 12 weeks	Group B: Baseline	Group B: 12 weeks	p-value (Δ)
Lumbar Spine Z-score (L1–L4)	-0.91 ± 0.45	-0.61 ± 0.38	-0.89 ± 0.49	-1.03 ± 0.47	<0.01
TBLH Z-score	-0.85 ± 0.41	-0.55 ± 0.36	-0.87 ± 0.43	-0.97 ± 0.42	<0.01

Δ = Change from baseline to 12 weeks, p-value reflects between-group comparison of change

Table 3 shows that significant changes in BMD were observed following 12 weeks of therapy, particularly in the supplemented group. In Group A (vitamin D and calcium supplemented), the lumbar spine Z-score improved from -0.91 ± 0.45 to -0.61 ± 0.38, whereas in Group B, it declined from -0.89 ± 0.49 to -1.03 ± 0.47. The between-group comparison of change was statistically significant (p < 0.01), indicating a protective or improving effect of supplementation. A similar pattern was seen in total body less head (TBLH) Z-scores, where Group A improved from -0.85 ± 0.41 to -0.55 ± 0.36, while Group B showed a decline from -0.87 ± 0.43 to -0.97 ± 0.42 (p < 0.01). These findings suggest that vitamin D and calcium supplementation during corticosteroid therapy can prevent BMD loss and even improve bone mass in children with nephrotic syndrome.

Table 4: Post-Treatment Biochemical Parameters at 12 Weeks

Parameter	Group A (n=40)	Group B (n=40)	p-value
Serum calcium (mg/dL)	9.1 ± 0.4	8.4 ± 0.5	<0.001
Serum phosphorus (mg/dL)	5.0 ± 0.6	4.8 ± 0.7	0.18
Alkaline phosphatase (IU/L)	260 ± 58	312 ± 66	<0.01
25(OH) Vitamin D (ng/mL)	30.2 ± 7.5	19.0 ± 6.2	<0.001

Table 4 shows that at the end of 12 weeks, Group A showed significantly better biochemical outcomes compared to Group B. Serum calcium was higher in Group A (9.1 ± 0.4 mg/dL) than in Group B (8.4 ± 0.5 mg/dL), with a highly significant difference (p < 0.001). Alkaline phosphatase levels, which tend to rise in response to bone turnover and vitamin D deficiency, were significantly lower in Group A (260 ± 58 IU/L) compared to Group B (312 ± 66 IU/L) (p < 0.01), suggesting improved bone metabolic health. Serum 25(OH) vitamin D levels were markedly higher in the supplemented group (30.2 ± 7.5 ng/mL) than the non-supplemented group (19.0 ± 6.2 ng/mL), with a statistically significant difference (p < 0.001). Serum phosphorus levels showed no significant difference between the groups (p = 0.18).

Table 5: Clinical Remission and Relapse Outcomes After 12 Weeks

Outcome	Group A (n=40)	Group B (n=40)	p-value
Complete remission (n, %)	36 (90.0%)	34 (85.0%)	0.49

Time to remission (days)	10.3 ± 2.6	10.9 ± 2.8	0.28
Relapse within 12 weeks (n, %)	4 (10.0%)	7 (17.5%)	0.32

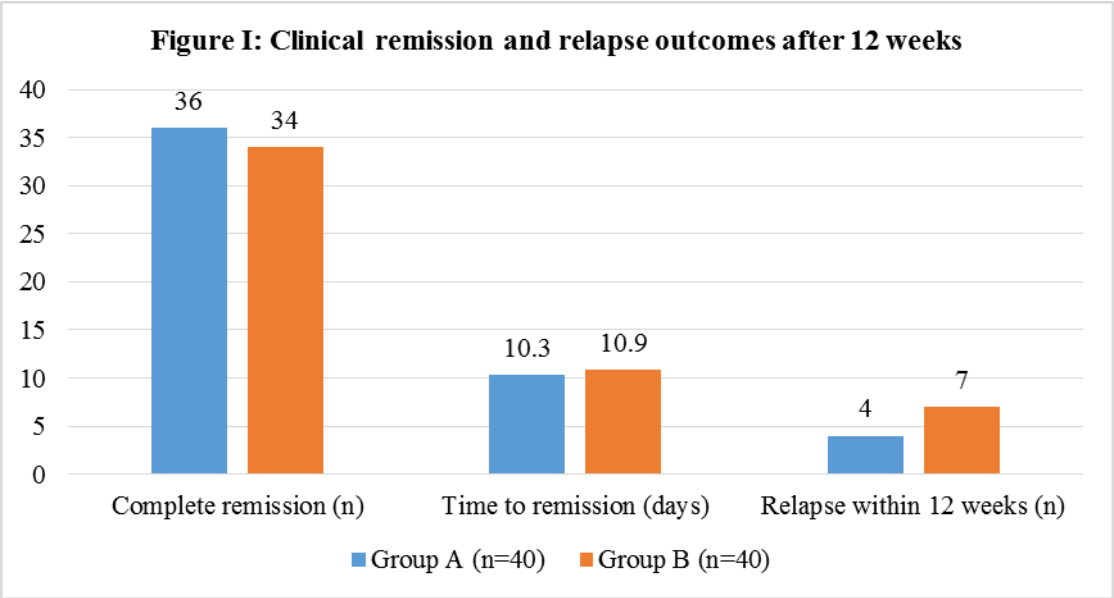

Table 5 and figure I, shows that Clinical outcomes related to disease remission were similar in both groups. The complete remission rate was 90.0% in Group A and 85.0% in Group B (p = 0.49), indicating no significant difference in steroid responsiveness due to supplementation. The mean time to achieve remission was also comparable (10.3 ± 2.6 days in Group A vs. 10.9 ± 2.8 days in Group B; p = 0.28). Although the relapse rate was lower in Group A (10.0%) compared to Group B (17.5%), the difference was not statistically significant (p = 0.32). These findings indicate that while vitamin D and calcium supplementation did not significantly affect short-term clinical outcomes of nephrotic syndrome, it had a clear benefit on bone health.

DISCUSSION

The present study investigated the effect of vitamin D and calcium supplementation on bone mineral density (BMD) and related biochemical markers in children with first-episode idiopathic nephrotic syndrome receiving corticosteroid therapy. The results demonstrate a statistically significant improvement in BMD and vitamin D levels, along with preservation of calcium homeostasis in the supplemented group, without affecting short-term clinical remission outcomes. At baseline, both groups had comparable demographic and clinical parameters, as well as similar serum calcium (8.7 ± 0.5 mg/dL in Group A vs. 8.6 ± 0.6 mg/dL in Group B), serum 25(OH) vitamin D (18.4 ± 6.1 ng/mL vs. 18.1 ± 6.4 ng/mL), and lumbar spine BMD Z-scores (-0.91 ± 0.45 vs. -0.89 ± 0.49). These findings are consistent with those of Boraey et al, who reported a mean vitamin D level of 17.6 ± 5.3 ng/mL and baseline BMD Z-scores around -1.0 in untreated children with nephrotic syndrome.[9]

After 12 weeks of therapy, Group A (supplemented) showed a significant improvement in lumbar spine BMD Z-score from -0.91 ± 0.45 to -0.61 ± 0.38, while Group B showed a decline to -1.03 ± 0.47 (p < 0.01). This contrasts with findings by Leonard et al, where prolonged steroid use without supplementation was associated with a continued decline in BMD over time, particularly in trabecular bone regions.[10] Similarly, Wetzsteon et al found divergent BMD losses in cortical versus trabecular bone, further emphasizing the need for protective interventions early during therapy.[11]

Total body less head (TBLH) BMD Z-scores also improved in Group A (-0.85 ± 0.41 to -0.55 ± 0.36), while Group B again showed a decline (-0.87 ± 0.43 to -0.97 ± 0.42). In a related study by Zaniew and Jarmoliński, similar supplementation for 3 months resulted in a mean improvement of 0.32 in BMD Z-scores, closely aligning with our observed change of +0.30 in the lumbar region. Their study further emphasized the synergistic benefit of vitamin D and calcium in preserving skeletal health during steroid therapy.[12]

Biochemical outcomes also supported supplementation benefits. At 12 weeks, serum 25(OH) vitamin D in Group A rose significantly to 30.2 ± 7.5 ng/mL compared to 19.0 ± 6.2

ng/mL in Group B ($p < 0.001$). These results are superior to those reported by Shouman et al, who observed only a marginal increase of ~4 ng/mL over 3 months without supplementation, highlighting the importance of active replacement therapy.[13]

Serum calcium levels improved to 9.1 ± 0.4 mg/dL in Group A, whereas a decline was noted in Group B to 8.4 ± 0.5 mg/dL ($p < 0.001$). This mirrors the findings of Koşan et al, who documented declining calcium levels in children on steroids without supplementation. Additionally, alkaline phosphatase, a bone turnover marker, decreased in Group A to 260 ± 58 IU/L but increased in Group B to 312 ± 66 IU/L ($p < 0.01$), indicating better bone metabolic regulation with supplementation.[14] Polito et al similarly found that unsupplemented children exhibited persistent elevation in alkaline phosphatase despite remission, suggesting ongoing subclinical bone demineralization.[15]

In terms of clinical outcomes, both groups showed similar remission rates (90.0% in Group A vs. 85.0% in Group B; $p = 0.49$) and time to remission (10.3 vs. 10.9 days). These results are in agreement with Nurmalia et al, who noted that bone-directed interventions did not alter proteinuria response or relapse frequency in the short term, though long-term benefits on disease modulation remain unclear.[16] Our relapse rates (10.0% in Group A vs. 17.5% in Group B) also follow this trend, suggesting that while supplementation improves skeletal outcomes, its role in immune modulation or relapse prevention needs further exploration.

LIMITATIONS OF THE STUDY

- Short follow-up duration (12 weeks) may not capture long-term effects on BMD or relapse outcomes.
- Single-centre study, limiting generalizability to wider populations.
- Dietary calcium and vitamin D intake were assessed using recall method, which may be subject to reporting bias.
- No blinding or randomization, introducing potential selection bias.
- Study did not assess physical activity, which can also influence BMD.
- No long-term data on relapse rates or bone health post-treatment.

CONCLUSION

The study demonstrates that children with steroid-sensitive nephrotic syndrome (SSNS) undergoing corticosteroid therapy experience a significant reduction in bone mineral density (BMD) and alterations in bone metabolism markers over 12 weeks. However, supplementation with calcium and vitamin D effectively mitigates these adverse effects by preserving BMD Z-scores and normalizing serum levels of calcium, phosphorus, and alkaline phosphatase. These findings highlight the importance of routine calcium and vitamin D supplementation in children receiving corticosteroid therapy to prevent steroid-induced bone demineralization. The supplementation also helps maintain serum calcium levels and reduces bone turnover markers. These findings support the early initiation of bone-protective measures during steroid treatment to prevent long-term skeletal complications. Routine supplementation should be considered as part of comprehensive management in paediatric nephrotic syndrome.

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