# **Original Research Article**

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# Biochemical bone markers in children with steroid sensitive nephrotic syndrome in remission

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#### **ABSTRACT**

**Background:** Glucocorticoids, the recommended first line treatment of steroid sensitive nephrotic syndrome (SSNS), are notorious for causing osteoporosis. There are very few studies from tropical countries looking at the lasting effects of a short course of glucocorticoids in SSNS. The objective is to study the effect of glucocorticoids and its dose on Vitamin D levels and biochemical markers of calcium metabolism in children with SSNS and to formulate a criterion to administer prophylactic calcium and vitamin D supplementation to such patients.

**Methods:** A cross-sectional case-control study was conducted on 30 children with SSNS in remission and 30 healthy controls. Serum levels of 25 hydroxycholecalciferol [25(OH)D], calcium, phosphorous, albumin, alkaline phosphatase (ALP) and intact parathyroid (PTH) were measured. Total glucocorticoid exposure during the illness was summarized.

**Results:** Children with SSNS had significantly lower height [median-100.00 (interquartile range {IQR}- 14.5) vs. controls [115.50 (17.5)] cm; P= 0.0003. Serum ALP levels was significantly higher in the cases [median 264 (IQR-80.7)] IU/L vs. controls [median 234 (IQR- 132)] IU/L; P= 0.028. Though hypovitaminosis D was universal in the study cohort; children with SSNS had worse Vitamin D status (76.7%) than healthy controls (50%). Levels of serum calcium, phosphorous, vitamin D and PTH were not significantly different between the two groups, nor were they related to total cumulative dose of steroid. Vitamin D levels showed no significant co-relation with number of relapses, age, calcium, phosphate, ALP, or PTH levels.

**Conclusions:** Children with SSNS may benefit from routine measurement of 25 (OH) D and prophylactic supplementation with calcium and Vitamin D.

Keywords: Glucocorticoids, Steroid sensitive nephrotic syndrome (SSNS), Vitamin D

### INTRODUCTION

In children, the most frequent glomerular disease is idiopathic nephrotic syndrome which involves histological abnormalities of the kidney including minimal changes, focal segmental glomerulosclerosis and diffuse mesangial proliferation. Nephrotic Syndrome (NS) often has a relapsing course and usually responds to steroids.

The loss of vitamin D metabolites in urine combined with the detrimental effect of corticosteroids (CS) often leads to disturbances in calcium (Ca) and vitamin D metabolism in nephrotic children.<sup>3</sup>

The onset and subsequent relapses of NS and its treatment may disrupt active bone formation and mineral deposition during childhood.<sup>4</sup>

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The loss of both 25(OH)D and its binding protein (DBP) in urine is responsible for the low levels of 25-hydroxycholecalciferol [25(OH)D] documented in NS patients during a relapse.<sup>5,6</sup> However, these low levels do not reflect steady state of body stores since most relapses are short-lasting.<sup>7,8</sup> The evidence on vitamin D levels during remission of NS remains mixed but since vitamin D deficiency may contribute to osteoporosis in NS, early detection and treatment is in order.<sup>4-6,9</sup> Present study looks into the probable lasting effect of glucocorticoids on vitamin D levels and biochemical markers of calcium metabolism in these children.

#### **METHODS**

This was a cross-sectional case- control study, carried out at a tertiary centre in Mumbai, India, and was approved by the institutional review board. Cases and healthy controls were recruited from the Pediatric Nephrology and general outpatient clinics respectively over a period of 18 months after obtaining parental written informed consent.

Based on the data from recent studies, examining 25(OH)D levels in NS remission, a sample size 30 cases with age and sex matched controls was considered appropriate. <sup>4,9,10</sup> Type 1 error (alpha) was set at 0.05 and Type 2 error (beta) was fixed at 0.2.

Subjects, between 2 to 10 years (y) of age with SSNS were included in the study provided they had received steroid therapy  $\geq 2$  months prior to the study visit. Subjects with steroid resistant nephrotic syndrome, on immunosuppressive drugs other than glucocorticoids, renal insufficiency (defined by glomerular filtration rate (GFR) <90 ml/min/1.73m2 of body surface area (BSA) as estimated by Schwartz formula), or other medical conditions unrelated to NS that could affect bone health, growth and vitamin D status, were excluded. 11

Negative or trace protein in urine was documented at the time of enrollment by the sulphosalycylic acid test. All children belonged to a comparable geographical location without substantial variation in sun exposure.

Serum 25(OH)D levels defining vitamin D status were adapted from the Institute of Medicine (IOM) recommendations and routinely accepted consensus statements (Table 1). 12,13

Table 1: Vitamin D status in Relation to 25(OH)D levels.

Vitamin D status	25(OH)D level, ng/ml (nmol/L)
Severe deficiency	<5 (12.5)
Deficiency	<15 (37.5)
Insufficiency	15-20 (37.5-50.0)
Sufficiency	>20 (50.0)
Risk of toxicity	>50 (124.8)

Medical charts of the SSNS children were reviewed for date(s) of diagnosis, last relapse, total number of relapses, renal biopsy results (where indicated), prior steroid sparing therapy and total glucocorticoid (prednisolone) exposure from the first dose to the last dose. Details of dietary supplementation were documented in all subjects. Definitions used for clarifying the course of NS were as per the guidelines of Indian Academy of Pediatrics. <sup>14</sup> Depending on their blood values, all participants were started on Vitamin D and calcium supplementation.

# Measurements and assays

Age and gender-specific standard deviation scores (z-scores) for height and weight were calculated using the WHO Child Growth Standards.<sup>15</sup>

Serum levels of total Calcium (Ca), phosphorous (P), albumin, alkaline phosphatase (ALP), were determined by methods adapted for the ADVIA 1800 Chemistry System. Circulating 25(OH)D and intact PTH concentrations were measured by chemiluminescence with Advanced Acridinium Ester Technology using the ADVIA Centaur® CP Immunoassay System. <sup>16</sup>

# Data analysis

Association between qualitative variables was assessed by Chi-Square test with Continuity Correction and Fisher's exact test where p-value of Chi-Square test was invalid due to small counts. Quantitative data was represented using Mean±SD, Median and Interquartile range (IQR). Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. Relationship between Quantitative data was assessed using Pearson's Correlation. Binary Logistic Regression was used to assess predictiveness of independent variables on 'Serum vitamin D status' among the cases. SPSS Version 17 was used for analysis

## **RESULTS**

Thirty SSNS patients and 30 controls were enrolled in the study. Males and females were equally distributed in present patient group.53.3% of SSNS children were in the age group 5-7 y. Median age at study entry was 6 y.

Seven children (23.3%) had their first episode of NS and 23 (76.6%) were infrequent relapsers. All were steroid sensitive. None of the subjects were frequent relapser or steroid dependent. Total number of relapses among cases was 45 with a mean of  $1.5\pm1.14$ .

Mean disease duration was 1.55±1.23 y with a maximum duration of 4 y since the first episode. 19 patients (63.3 %) were on calcium supplementation and none on vitamin D supplementation. NS children had a significantly lower height (mean 104.95±9.93 cm, P=0.003) than controls (115.63±11.54), consequently

resulting in a significant difference in the BSA (P = 0.00375).

Vitamin D levels were not significantly different between cases (13.88±5.39) and controls (14.62±4.45). Levels of serum calcium, phosphorous, creatinine, BUN and albumin were within normal range in both cases [Ca 9.28±0.34, P 4.29±0.45, creatinine 0.58±0.14, BUN 18.23±6.68, albumin 3.47±0.30] and controls [Ca 9.35±0.35, P 4.22±0.47, creatinine 0.56±0.18, BUN 16.49±8.03, albumin 3.44±0.27] (Table 2).

Table 2: Comparison of various variables between cases and controls.

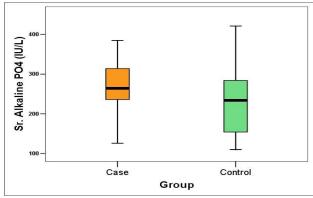
Variables	Cases n=30 (mean±SD)	Controls n=30 (mean±SD)	p-value
Age ^ (years)	5.58±1.50	5.58±1.50	1.00
Weight (kg)	18.25±3.94	20.58±4.89	0.047
Height (cm)	104.95±9.93	115.63±11.54	0.0003
S. Vitamin D^ (ng/ml)	13.88±5.39	14.62±4.45	0.279
Total Protein (g/dl)	6.43±0.35	6.24±0.34	0.0414
Albumin (g/dl)	3.47±0.30	3.44±0.27	0.674
S. Calcium ^ (mg/dl)	9.28 ±0.34	9.35±0.35	0.541
S.Phosphoro us^ (mg/dl)	4.29±0.45	4.22±0.47	0.561
BUN (mg/dl)	18.23±6.68	16.49±8.03	0.365
S. Creatinine (mg/dl)	0.58±0.14	0.56±0.18	0.639
S. Alkaline PO4 (IU/L)	272.93±59.3 1	231.10±82.37	0.028

<sup>^</sup>Data failed 'Normality' test. Hence Mann-Whitney test applied.

Serum ALP was significantly higher in cases (mean 272.9 $\pm$ 59.3) as compared to controls (231.1 $\pm$ 82.3) (P = 0.028). However, the mean value in both groups was in normal range (Figure 1).

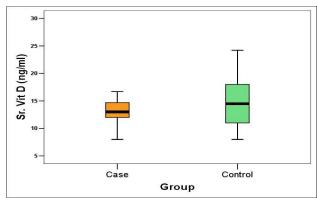
Hypocalcaemia was present in 16.7% (n =5) of children with SSNS as compared to 13.3 % (n=4) in controls. No association was found between calcium supplementation and serum calcium levels.

Serum phosphorous level was high in 40% (n=12) of cases as compared to 30% (n=9) in controls (P=0.588). Two SSNS children had increased PTH values, of which only 1 had vitamin D deficiency. With both cases and controls taken together, 53 children had a vitamin D value below 20 ng/ml (n=53) (Figure 2).



The horizontal lines within each box designate the median values, the lower and upper horizontal lines at the top and bottom of the boxes delineate the 25th and 75th percentiles, and the whiskers mark the upper and lower adjacent values.

Figure 1: Box and Whisker plot of Sr. alkaline PO4 (IU/L) in cases and controls.



Box and whisker plots of 25-hydroxyvitamin D [25(OH)D] concentrations in controls and patients with steroid-sensitive nephrotic syndrome (SSNS). The horizontal lines within each box designate the median values, the lower and upper horizontal lines at the top and bottom of the boxes delineate the 25th and 75th percentiles, and the whiskers mark the upper and lower adjacent values.

Figure 2: Box and Whisker plot of Sr. Vitamin D (ng/ml) in cases and controls.

71.7% had vitamin D deficiency whereas the rest were insufficient. Amongst cases, 23 children had vitamin D deficiency and 3 children had vitamin D level in the insufficient range. The control group had 15 children with vitamin D deficiency and 12 children with insufficiency. This difference was significant (P=0.019) (Figure 3). 19 NS children were on calcium supplementation, of which 2 had hypocalcemia. Of the remaining 11 cases, 3 had hypocalcemia (P=0.327). Of the 7 children enrolled after their first episode, 6 had vitamin D deficiency (85.71%) and 1 child had vitamin D insufficiency. 8 cases had a single relapse. 6 (75%) of them had vitamin D deficiency. 9 cases had 2 relapses, of which 7 (77.7%) had vitamin D deficiency. Of the 5 cases who had 3 relapses, 4 (80%) had vitamin D deficiency. Vitamin D level was 25.8 ng/ml in the single case with 4

relapses. No significant association was found between the number of relapses and vitamin D levels (P= 0.598).

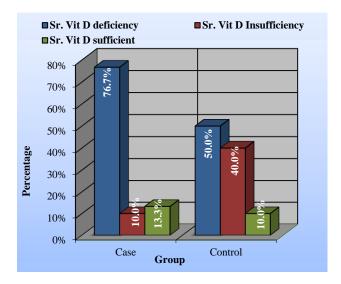


Figure 3: Serum Vitamin D level among cases and controls

Serum ALP was found to be high in only 4 (13.3%) cases, of which 3 had vitamin D deficiency and 1 case had vitamin D insufficiency. 20 cases with vitamin D deficiency were found to have normal ALP levels (P=1).

The mean dosage of prednisolone was 26.04±5.65 mg/day. The cumulative prednisolone dose administered between the date of diagnosis of NS and remission was 3528.83±1189.45 mg, maximum being 6430mg.

Variables such as age, cumulative dose of prednisolone, height, serum ALP and PTH levels were not found to be independent predictive factors for vitamin D deficiency.

## **DISCUSSION**

NS children are prone to biochemical derangements in vitamin D and calcium metabolism caused by the disease as well as glucocorticoid therapy. Research from tropical countries is lacking in this cohort.<sup>10</sup>

NS is more common in boys.<sup>4,10,17</sup> The equal distribution of males and females in present cohort may be due to the small sample size and heterogeneity.

More than 50% of the cases were in the 5-7 y age group highlighting the typical age presentation in SSNS. 4.17 25(OH)D levels has been correlated negatively with age. 9.10 However, authors found no correlation between them in either of presentstudy arms. This effect may be secondary to the narrow and younger age range (between 3-8 y) of the subjects enrolled.

76.6% of cases were infrequent relapsers. Frequent relapsers are more likely to be on immunosuppressant drugs or have an underlying renal pathology other than

minimal change disease which may affect the levels of biochemical markers. Biyikli et al compared frequent and infrequent relapsers and found that higher cumulative dose of prednisolone caused a greater variation in biochemical parameters. The maximum cumulative dose of prednisolone seen in presentstudy was 6430 mg with no significant correlation between prednisolone dosage and various biochemical markers. The maximum number of relapses seen in any case was 4, and only infrequent relapsers were part of the study group thereby decreasing the cumulative prednisolone dosage they might have been exposed to.

SSNS children had significantly lower weight (18.25±3.94kg) as compared to controls (20.58±4.89kg) [P=0.047]. Though authors had conflicting results, the mean values of both were very close to each other. Patients also had significantly lower height (P=0.0003), which is consistent with the expected side effect of glucocorticoids. 17

Several reports have documented the levels of ALP in SSSN. While studies reporting lower levels of ALP have attributed it to the detrimental effect of steroids on osteoblasts, Kosan et al found increased ALP levels in their study group which may be due to increased bone turnover. 4,10,19 Low ALP levels have also been correlated to the cumulative glucocorticoid dose, being more prevalent in frequent relapsers as compared to infrequent relapsers. 4 Though authors found significantly higher ALP levels in cases (mean 272.9±59.3) when compared to controls (mean 231.1±82.3), it was well within the normal range (P=0.028). No significant correlation was found between vitamin D and ALP levels in presentcase group.

Vitamin D deficiency results in hypocalcemia due to a decrease in intestinal calcium absorption. This in-turn leads to PTH secretion, increased conversion of 25(OH)D to 1,25(OH)2D resulting in calcium reabsorption and phosphate loss from renal tubules, thereby reducing bone mineralization.<sup>20</sup> Authors did not find any correlation of 25(OH)D levels with serum calcium, phosphate, or PTH. Though not significant, 40% SSNS children had high serum phosphorous levels. This may be due to normalization of the transiently altered calcium balance resulting from defective intestinal absorption and diminished bone sensitivity to calcemic action of PTH.5 Authors found no statistical difference in PTH levels cases and controls. Secondary hyperparathyroidism is rarely seen in nephrotic children. Freundlich et al published the first study in which half of the SSNS children had secondary hyperparathyroidism.<sup>5</sup> In the study done by Biyikli et al, none of the patients, even those with severe vitamin D deficiency, had high PTH levels.4 CS use may result in an early and accelerated bone resorption. This is probably due to an increase in osteoclasts mediated through the osteoblast receptor activator of the nuclear factor k-B ligand, independent of PTH.21 This mechanism may play a

protective role in maintaining normal levels of PTH in NS despite vitamin D deficiency and CS therapy.

Weng et al reported that children with remitted NS have worse vitamin D status than healthy controls. Both Freundlich et al and Huang et al concluded that low 25(OH)D levels during relapse normalized quickly postremission, after the resolution of proteinuria and loss of DBP. Banerjee et al reported that serum 25(OH)D levels remain low for about 3 months after NS relapse and subsequently increase to control levels with longer duration of remission. Biyikli et al showed that even though 25(OH)D levels increased after remission, they are still lower than those in controls at 3 months. This was more significant in frequent relapsers which they attributed to higher proteinuria.

Repeated episodes of proteinuria are most likely responsible for low 25(OH)D levels seen in children with SSNS who are in remission.<sup>22</sup> Though the response to glucocorticoids is reliable during a relapse, it is not always instantaneous, and proteinuria may actually persist for weeks before resolving.<sup>23,24</sup> Multiple episodes of relapses result in recurring periods of prolonged proteinuria which may eventually lead to low serum 25(OH)D levels. In frequent relapsers, vitamin D levels may not get enough time to normalize before another relapse.

It was interesting to note that children in both study groups had a vitamin D level <30 ng/dl. Several studies have reported that seemingly healthy children often have hypovitaminosis D.<sup>25-27</sup> Although in present study, healthy controls had a high prevalence of suboptimal 25(OH)D levels, 76.7% of SSNS children had vitamin D deficiency whereas only 50% of the control group children were deficient. 40% of the healthy controls had vitamin D insufficiency as compared to only 10% in case group. Thus, though hypovitaminosis D was present uniformly, children with SSNS seemed to be more severely affected.

Routine measurement of serum 25(OH)D may be needed in NS children, many of whom may benefit from vitamin D repletion. NKF (National Kidney Foundation) guidelines recommend high-dose supplementation with ergocalciferol (vitamin D2) for at least 6 months in persons with GFR <60 ml/min, elevated PTH and serum 25(OH) levels <30 ng/ml.<sup>28</sup> It is unclear, however, whether the guidelines are applicable to nephrotic children with decreased 25(OH)D but normal GFR and PTH.

# **CONCLUSION**

Present study shows that vitamin D levels in children with SSNS become similar to healthy controls after 2 months of remission, though they seemed to be more severely affected.

The cross-sectional design of present study limits us from predicting causality of unfavorable vitamin D status. A prospective, longitudinal study design measuring circulating 25(OH)D levels before and after onset of SSNS would be more suitable. Diet and sunlight exposure may confound the relationship between SSNS and 25(OH)D, and only limited information regarding dietary supplementation and no information regarding sunlight exposure was collected.

Although guidelines on NS treatment recommend calcium supplementation for children on long-term steroids, it remains a dilemma whether vitamin D supplementation should be started as well. <sup>14</sup> Keeping the potential side-effects of vitamin D and calcium supplementation like hypercalcemia, hypercalciuria and nephrolithiasis in mind, it seems prudent to treat SSNS children with low dose vitamin D (400IU) and calcium supplements (1g) daily. Vitamin D levels should be evaluated before starting the steroid treatment with regular follow up for early detection of vitamin D insufficiency which may then be adequately treated.

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Ethical approval: The study was approved by the Institutional Ethics Committee and in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

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