

Original Article

# Investigating Hypovitaminosis D and Childhood Nephrotic Syndrome: An Observational Study to Find Subjects in Need of Attention



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## ABSTRACT

**Background and Aim:** Nephrotic syndrome (NS) is associated with variable ranges of vitamin D deficiency in the pediatric population. This study examines the vitamin D status in children with NS during active disease in a tertiary care center in eastern India.

**Methods:** This observational study was conducted for 18 months in a tertiary care hospital taking 60 cases of NS of 2-12 years of age and 30 age- and sex-matched controls. Serum 25(OH) vitamin D and alkaline phosphatase (ALP) levels were assayed and analyzed.

**Results:** In this study, the mean vitamin D level ( $12.54 \pm 6.85$  ng/mL) in cases was significantly lower ( $P=0.002$ ) compared to the control group ( $22.1 \pm 5.8$  ng/mL). Mean vitamin D level was low in all groups of NS cases and the lowest in steroid-resistant NS (SRNS) followed by steroid-dependent NS (SDNS)/frequent relapse NS group. Vitamin D insufficiency ( $12-20$  ng/mL) was more prevalent in the first episode whereas deficiency ( $<12$  ng/mL) was more common in subjects with relapse. Serum ALP levels were raised in 35% of vitamin D deficient cases but normal in the rest of the deficient, all insufficient, and sufficient cases.

**Conclusion:** Hypovitaminosis D was more common in children with NS as compared to the general pediatric population irrespective of sex. Vitamin D status varied according to the course of the disease of NS. A strong negative correlation of vitamin D status and serum ALP was observed in children with NS but serum ALP level for screening of vitamin D status could not be used.

**Keywords:** Nephrotic syndrome (NS), Children, Hypovitaminosis D, Deficiency, Alkaline phosphatase



## Introduction

**N**ephrotic syndrome (NS) is a common renal disease with an estimated annual incidence of 2-7 per 100000 children, starting between 2 to 6 years of age [1-4]. In studies with primary and secondary NS, vitamin D deficiency ranges from 20% to 100% compared to 9% to 18% in the general pediatric population [3, 5-7]. This wide variation of prevalence of vitamin D deficiency in children with NS in different studies from different parts of the world was probably due to different factors influencing vitamin D status in children in different geographical areas and the different subcategories of NS prevalent among children who were included in those studies. Initially, these abnormalities were thought to be transient and resolved with remission; however, recent data suggest that vitamin D deficiency persists despite achieving remission [5, 8]. Abnormal vitamin D metabolism in NS is multifactorial with contributions from losses of vitamin D binding protein and vitamin D in urine and these urinary losses of vitamin D binding protein can be secondary to proteinuria, overwhelming the proximal convoluted tubule resorption via megalin and cubulin pathways [9-11]. Whether vitamin D status influences the course of illness of NS is still unknown. Deficiency in vitamin D may lead to hypocalcemia, hyperparathyroidism, and diminished bone mineral density. The impact of 25(OH) vitamin D deficiency on the bones in children with NS is further complicated by repeated exposure to corticosteroids. Steroids chelate with calcium in the patients treated with NS making the bones fragile. Vitamin D deficiency in children of NS who are prone to steroid-induced osteoporosis increases the risk of fragile bone disease and its related complications.

There is a significant gap in knowledge about vitamin D levels in children with NS in this region of eastern India. Accordingly, this study assesses the vitamin D status in children with NS during active disease in a tertiary care center in eastern India. The other objectives are to see any variation of vitamin D status with different categories of NS according to the course of the disease and to find any correlation of vitamin D status with serum alkaline phosphatase (ALP) in these children.

## Materials and Methods

This cross-sectional observational study was conducted in the Department of Pediatric Medicine in a tertiary care hospital in Kolkata, West Bengal, India over 18 months with prior approval by the Institutional Ethics Committee. Consecutive 60 children with 2-12 years of

age, attending this department with idiopathic NS were included in the study after taking written informed consents from the guardians and assents from the patients where applicable. Patients receiving megadose of vitamin D in the last 6 months, having renal insufficiency (glomerular filtration rate  $<90$  mL/min/1.73 m<sup>2</sup> estimated from the level of serum creatinine and height by Schwartz formula), known chronic liver or bone disease and congenital NS were not included in this study. A total of 30 age- and sex-matched children who attended the Outpatient Department for follow-up after recovery from minor illness without a history of renal, liver, or bone disease and not having vitamin D supplementation in the last 6 months were selected as controls. All study populations were evaluated and treated for the presenting illness and data were entered into the pre-structured questionnaire. Based on the clinical history and past treatment records study population was grouped as first episode NS, infrequent relapse NS (IFRNS), frequent relapse NS (FRNS), steroid-dependent NS (SDNS), and steroid-resistant NS (SRNS) as per the standard definitions [2]. Serum 25(OH) vitamin D levels were measured by nephelometric method and serum ALP levels with the [International Federation of Clinical Chemistry \(IFCC\)](#) enzymatic method with p-nitrophenyl phosphate as the substrate and diethanolamine as the buffer in the institutional laboratory before starting treatment with corticosteroids during their active stage of the disease. Serum 25(OH) vitamin D levels of controls were also measured. Serum vitamin D levels defining vitamin D status were adapted from the prevention and treatment of vitamin D and calcium deficiency in children and adolescents: [Indian Academy of Paediatrics \(IAP\)](#) guidelines, where deficiency, insufficiency, and sufficiency was defined as serum 25(OH) vitamin D level  $<12$  ng/mL ( $<30$  nmol/L), 12-20 ng/mL (30-50 nmol/L) and  $>20$  ng/mL ( $>50$  nmol/L), respectively [12]. ALP levels of controls were not measured.

Serum ALP levels of cases were compared with the available data published in literature mentioning Mean $\pm$ 2 standard deviation values for the age and sex derived from a large sample of 1741 healthy children and adolescents where the biochemical reagents (substrate and buffer) used for the assay were similar to our laboratory reagent [13].

For statistical analysis, the data were entered into a Microsoft Excel spreadsheet and then analyzed by Statistica software, version 6. The data had been summarized as Mean $\pm$ SD for numerical variables and count and percentages for categorical variables. Comparison of normally distributed numerical variables between

**Table 1.** Association between vitamin D status and category of course of NS

Vitamin D Status	No. (%) / Mean ± SD				P
	First Episode (n=26)	IFRNS (n=11)	FRNS/SDNS (n=19)	SRNS (n=4)	
Deficient	2(7.7)	3(27.3)	17(89.5)	4(100)	-
Insufficient	18(69.2)	5(45.5)	2(10.5)	0	-
Sufficient	6(23.1)	3(27.3)	0	0	-
Vitamin D (ng/mL)	16.83±5.76	14.9±4.9	7.27±3.2	3.57±1.2	<0.00001

Abbreviations: IFRNS: Infrequent relapse nephrotic syndrome; FRNS: Frequent relapse nephrotic syndrome; SRNS: Steroid-resistant nephrotic syndrome.

2 subgroups was done by Student's unpaired t-test. A comparison of skewed numerical variables between 2 subgroups was done by the Mann-Whitney U test. Comparison of proportions/percentages between 2 or more groups was done by chi-square test. Comparison of mean between more than two groups was done by analysis of variance test. Meanwhile,  $P \leq 0.05$  was considered statistically significant.

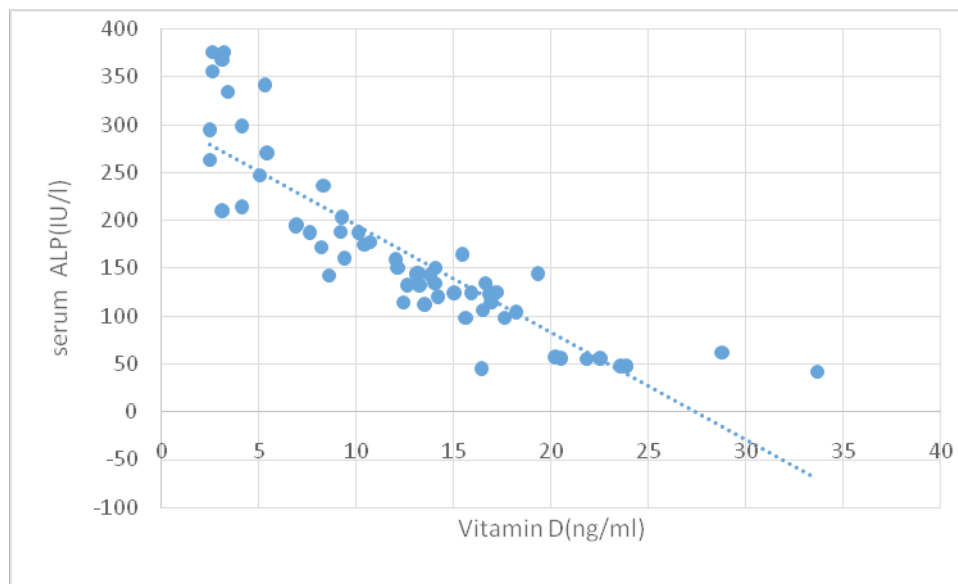
## Results

In this study, the mean age in cases and controls was  $6.6 \pm 2.9$  years and  $6.13 \pm 2.8$  years, respectively. Among the cases, 35 out of 60 (58.33%) belonged to the age group of 2-5 years and 25 (41.66%) were in the age group of 5-12 years. Vitamin D deficiency was equally prevalent (50%) in under 5 years and older children but insufficiency was more prevalent among under 5-year-olds (60% vs 40%). Half the cases were male whereas in control they accounted for 56.7% of the population. In our cohort, 26 (43.33%) belonged to the first episode NS, 11 (18.33%) to IFRNS, 19 (31.6%) to FRNS/SDNS, and the rest 4 (6.66%) to SRNS group. Among cases, mean vitamin D level was 12.7 ng/mL in males and 12.39 ng/mL in females. The same values in the control group were 21.5 ng/mL in males and 22.9 ng/mL in females. There was no statistically significant difference in mean vitamin D levels between males and females in both cases and controls. However, the mean vitamin D level ( $12.54 \pm 6.85$  ng/mL) in cases was significantly lower ( $P = 0.002$ ) compared to the control group ( $22.1 \pm 5.8$  ng/mL). Vitamin D levels were low ( $< 20$  ng/mL) in 85% of cases as compared to 23.3% of controls in this series ( $P < 0.05$ ). Among cases, vitamin D status was deficient in 43.3%, insufficient in 41.7%, and sufficient in 15%. Whereas in controls, vitamin D status was deficient in 6.6%, insufficient in 16.7%, and sufficient in 76.7%. Meanwhile, vitamin D status was deficient in 7.7%, insufficient in 69.2%, and sufficient in 23.1% of cases of

the first episode NS as compared to 66.7%, 23.3%, and 10%, respectively in the subjects with relapse. Thus, vitamin D insufficiency was more common in the first episodes but deficiency was more common in NS relapse. Among relapsers, 89.5% cases of the FRNS/SDNS group and 27.3% cases of IFRNS had deficient status of vitamin D. Mean vitamin D level was low in all groups of NS cases and the lowest in SRNS  $<$  SDNS / FRNS  $<$  IFRNS  $<$  first episode (Table 1). Serum ALP levels were raised ( $> 2$  standard deviations for age and sex) in 35% and normal in 65% of cases of NS with vitamin D deficiency. All cases of NS with vitamin D insufficiency and sufficiency had normal ALP levels. A strong negative correlation between vitamin D and ALP level was found in this study by calculating Pearson's correlation coefficient in the scatter plot (Figure 1).

## Discussion

In this study, we observed the mean vitamin D level in cases and control was  $12.54 \pm 6.85$  ng/mL and  $22.1 \pm 5.8$  ng/mL, respectively. In a similar type of study, Weng et al. observed a mean vitamin D level of  $17.4 \pm 7.6$  ng/mL in study cases and  $23.9 \pm 10.3$  ng/mL in controls [14]. The poor vitamin D status in children with NS was reflected in different studies [15, 16]. Among cases, mean vitamin D levels were 12.7 ng/mL in males and 12.39 ng/mL in females, showing almost similar levels which was also observed in studies done by Weng et al. [14] and Illalu et al. [6]. In our study vitamin D levels were low ( $< 20$  ng/mL) in 85% of cases as compared to only 23.3% in controls. Vitamin D deficiency was present in 43.3% and insufficiency in 41.7% of cases as compared to 6.6% and 16.7% in controls respectively ( $P < 0.05$ ). Vitamin D deficiency and insufficiency were almost equally prevalent among cases in our study. Illalu et al. [6] and Solanki et al. [7] found more cases of deficiency whereas Weng et al. [14] showed more cases of insufficiency in children with NS in their studies. These variations may be



**Figure 1.** Scatter plot showing strong negative correlation between serum vitamin D and ALP levels

Notes: The Pearson correlation coefficient ( $r$ )=-0.78.

due to different geographical areas with variable vitamin D status in general. In this study vitamin D status was compared between the first episode NS and NS relapsers and we found 69.2% of the first episode NS had insufficiency of vitamin D but almost in the same tune, 66.7% of relapsers had deficiency of vitamin D. Mean vitamin D levels in the first episode NS and relapsers were 16.83 ng/mL and 11.4 ng/mL, respectively. A similar study by Illalu et al. [6] showed deficiency was more common in the first episode than relapse. Freundlich et al. [17] reported mean vitamin D (9 ng/mL) in relapse NS, almost similar to our observations. In this study prevalence of deficiency was higher in the order of SRNS > FRNS / SDNS > IFRNS > first episode and insufficiency was more prevalent in the order of first episode > IFRNS > FRNS / SDNS. Our study showed that the higher the intensity of the course of the disease, the greater the severity of hypovitaminosis D in children with NS. In this study number of cases of SRNS was only 4 and vitamin D status was deficient in all of them. This sample size of SRNS was too small to analyze. ALP levels were raised in 35% of cases with vitamin D deficiency but normal in rest as well as in all cases with vitamin D insufficiency and sufficiency. The scatter plot (Figure 1) shows the relationship between serum vitamin D and ALP levels of cases in this study where we observed a strong negative correlation ( $r$ =-0.78) unlike the study by Illalu et al. where they showed weak correlations [6].

## Conclusion

Hypovitaminosis D was more common in children with NS as compared to the general pediatric population irrespective of sex. Vitamin D status varied according to the course of the disease of NS, insufficiency was more common in the first episode of NS and deficiency in relapse NS. Among relapsers, almost 90% of the FRNS/SDNS group of children had vitamin D deficiency. There was a strong correlation of vitamin D deficiency with increased serum ALP but the normal level of ALP could not eliminate vitamin D insufficiency or even deficiency status in children with NS. Hence screening for subnormal vitamin D status by estimation of serum ALP in children with NS could not be used.

To conclude, considering the high prevalence of vitamin D deficiency among NS relapsers who are also in need of prolonged steroid therapy leading to vulnerability for bone fragility, the estimation and supplementation of vitamin D in cases of relapse NS especially FRNS/SDNS group should improve the quality of care in these children if the observations of our study is further supported by multicenter study with large sample size.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Conflict of interest

The author declared no conflict of interest.

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