

# **A High Prevalence Of Vitamin D Deficiency In Children With Steroid Sensitive Nephrotic Syndrome**

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## **ABSTRACT**

### **Background**

Vitamin -D deficiency (VDD) is very high in developing countries including Pakistan. Children with steroid- sensitive nephrotic syndrome(SSNS) are at risk of VDD and it may contribute significantly to morbidity and mortality in nephrotic children. Therefore, it is vital to study vitamin D levels in these children for future interventions.

### **Objective**

To determine VD status in children with steroid sensitive nephrotic syndrome.

### **Methods**

This cross- sectional study on 70 children with SSNS, conducted at National Institute of Child Health (NICH), Karachi from December 2014 - July 2015. Children aged 4-15 years, with SSNS, had more than two relapses and in remission state were included. Patients with active nephrotic state and on VD treatment or received VD in last two weeks were excluded. Serum VD level was measured by Enzyme Linked Immunosorbent Assay (ELISA) and outcome was categorised as sufficiency ( $\geq 30$  ng/ml), insufficiency ( $< 30$ ), deficiency ( $< 20$ ) and severe deficiency ( $< 10$  ng/ml). Demographics like age, gender, weight, height, body mass index (BMI), disease duration, VD level and outcome was collected and analysed on SPSS 20 using descriptive statistics.

### **RESULTS**

Among 70 children studied, mean age was  $9.69 \pm 3.31$  years and 60% were below 10 years. There was a male preponderance (67%). Mean weight, height and BMI was  $28.24 \pm 9.76$  Kg ,  $122.82 \pm 16.76$  cm and  $18.27 \pm 3.89$  Kg/m<sup>2</sup> respectively. Mean duration of disease was  $5.73 \pm 3.13$  years. Mean VD level was  $13.27 \pm 7.11$  ng/ml. There was suboptimal VD status in 95.71% of cases and it was severe VDD in 37%.

### **Conclusion**

Our findings of suboptimal VD status in 95.71% of children with SSNS are consistent with VD status in children with various disorders other than SSNS. Majority of children were either VD deficient (51.4%) or severely deficient (37.1%). Further prospective studies on large scale are needed to assess the VD deficiency, its relationship with steroid use and response to VD supplement in children with SSNS.

**Key words:** *Steroid Sensitive Nephrotic Syndrome, serum 25-OHD level, vitamin D status.*

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## **INTRODUCTION**

Childhood nephrotic syndrome is a disease of relapse and remission. The reported annual incidence of nephrotic syndrome is 2-7 cases per 100,000 children younger than 16 years and prevalence is 16 cases per 100,000 children.<sup>1</sup> There is epidemiological evidence of a higher incidence of nephrotic syndrome in children from South Asia.<sup>2</sup>

Corticosteroids are the mainstay of treatment for NS. Majority of children are steroid sensitive, however almost 60-80% relapse during course of their illness. Children with relapsing course are classified as infrequent, frequent (50-60%) and steroid dependent (40-50%) according to frequency of relapses.<sup>2-4</sup> Both FR and SD children are exposed to repeated high doses of steroids which predispose children to various complications like severe infections, growth retardation, obesity, behaviour problem, poor bone health including vitamin D and calcium disturbances.<sup>3,4</sup>

Vitamin D has an important role not only in bone health, but in many other diseases including cardiovascular, autoimmune diseases and cancers in adults and children.<sup>5</sup>

Recently vitamin D insufficiency and deficiency has emerged as significant health problem in all ages groups including adults, women and children.<sup>6-10</sup> Several studies have documented low serum vitamin D levels in 30-90% of paediatric population including children with chronic kidney disease and nephrotic syndrome.<sup>11-13</sup>

We know that prolonged and repeated use of steroids in NS increases the risk of vitamin D deficiency.<sup>14,15</sup> Long term glucocorticoids and suboptimal VD status in children with nephrotic syndrome may result in recurrent infections, bone pain and increased risk of fractures.<sup>14-16</sup> Most recent studies have suggested beneficial effects of use of Vitamin D supplements in children with nephrotic syndrome.<sup>17,18</sup>

Serum 25 hydroxy vitamin D (25-OHD) level is considered as stored form of vitamin D and its level reflects the adequacy of vitamin D status. Vitamin D status is affected mainly by ultraviolet sunlight, dietary intake and absorption as well hepatic and renal activation of 25-OHD.<sup>5,10</sup>

Currently, there is no consensus on vitamin D status and different studies have considered different levels for VD insufficiency and deficiency. Most of the guidelines suggest that 25-OHD level <30 ng/ml is insufficiency and <20 ng/ml as deficiency.<sup>19,20</sup>

There are some studies carried out in Pakistan on vitamin D status in children with rickets, respiratory tract infections, tuberculosis, growing pain and chronic kidney disease.<sup>8,11,12</sup> But no local study has been carried out so far to our knowledge about VD Status in children with SSNS. So, we under took this study to estimate the magnitude of vitamin D status in children with SSNS. This study may help in planning a policy to screen and supplement vitamin D in children with SSNS to minimize the morbidity associated with suboptimal vitamin D status.

The objective of our study was to determine Vitamin D status in children with steroid sensitive nephrotic syndrome.

### **Methods:**

This was a cross sectional study on 70 children with SSNS, conducted in the Department of Pediatric Nephrology of National Institute of Child Health (NICH), Karachi from December 2014 to July 2015. All children, aged 4-15 years with SSNS of more than 2 years duration attending the OPD, had more than two relapses during course of disease and were in remission state with varying oral maintenance dose of steroid at the time of enrolment, were studied. Children who were on VD supplementation in either form (oral or injectable) or received VD during last 2 weeks for rickets or any other reason. Informed consent was taken from parents/caregivers of all participating children and approval from institutional ethical committee was taken before enrolment.

### **Definitions:**

- (i) Remission of NS was defined as disappearance of oedema and proteinuria with daily oral steroid treatment.
- (ii) Relapse was defined as reappearance of oedema and proteinuria of 3+ or spot urine protein to creatine ration of  $\geq 2$ .
- (iii) Vitamin D status: VD status was categorised as sufficiency ( $\geq 30$  ng/ml), insufficiency (< 30 ng/ml), deficiency (<20 ng/ml) and severe VD deficiency (< 10 ng/ml).<sup>19</sup>

Serum vitamin D level(25-OHD) was measured by Enzyme Linked Immunosorbent Assay (ELISA) in NICH laboratory using standard technique.

### **Data collection & analysis:**

Patient's demographics like age, gender, weight, height, body mass index (BMI), duration of disease, 25-OHD level and category of VD status of all patients was collected and analysed on SPSS 20 using descriptive statistics. Mean and standard deviation (SD) was calculated for age, duration of disease, weight, height and BMI of the patients and vitamin D levels. Frequency and percentages were calculated for gender and vitamin D status (vitamin D sufficiency, insufficiency and deficiency). Effect modifiers like age, gender, BMI, duration of disease was controlled through stratification to see the effects of these variables on outcome. Chi -square test was applied to compare VD status categories with variables like age groups and gender. P value  $\leq 0.05$  was taken as significant.

## **RESULTS**

### **Characteristics of study participants**

**Table 1** shows the general characteristics of 70 children with steroid sensitive nephrotic syndrome. Mean age of the patients was  $9.69 \pm 3.31$  years, with range of 4-15 years. Majority of the patients 42 (60%) were below 10 years of age. There was a male preponderance (67.10%). Mean weight and height of the patients was  $28.24 \pm 9.76$  Kg and  $122.82 \pm 16.76$  cm. Majority (68.60%) of the study participants were  $\leq 30$  Kg and their height was  $< 120$  cm in 54.30% cases. Mean BMI was  $18.27 \pm 3.89$  Kg/m<sup>2</sup> and majority had BMI  $\leq 18.5$  kg/m<sup>2</sup>.

Mean duration of disease from diagnosis till the time of enrolment was  $5.73 \pm 3.13$  years and it was  $\leq 6$  years in 47 patients (67.10%).

**Table 1:** General characteristics of the patients with Steroid Sensitive Nephrotic Syndrome(n=70)

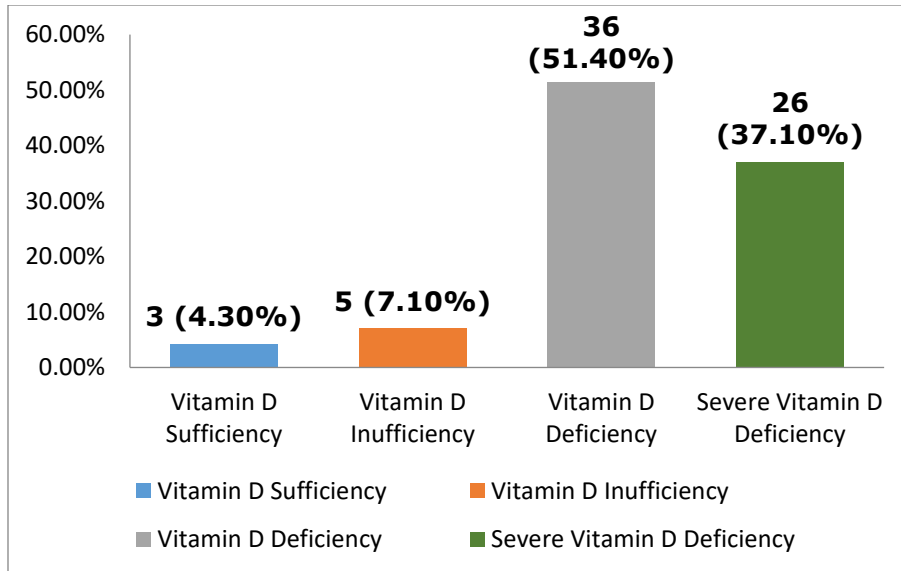
<b>Variable</b>	<b>Mean <math>\pm</math>SD</b>	<b>Minimum</b>	<b>Maximum</b>
<b>Age (yrs)</b>	<b>9.69 <math>\pm</math>3.31</b>	<b>4</b>	<b>15</b>
<b>Weight (Kg)</b>	<b>28.24 <math>\pm</math>9.76</b>	<b>2</b>	<b>60</b>
<b>Height (cm)</b>	<b>122.82 <math>\pm</math>16.76</b>	<b>96</b>	<b>157</b>
<b>BMI (kg/m<sup>2</sup>)</b>	<b>18.27 <math>\pm</math>3.89</b>	<b>1.60</b>	<b>26.70</b>
<b>Disease duration (yrs)</b>	<b>5.73 <math>\pm</math>3.13</b>	<b>2</b>	<b>13</b>
<b>25-OHD level (ng/ml)</b>	<b>13.27 <math>\pm</math>7.11</b>	<b>4.20</b>	<b>38.60</b>

BMI= body mass index, SD=standard deviation

### **Vitamin D status in study participants with steroid sensitive nephrotic syndrome:**

Vitamin D status in children with SSNS is shown in Fig I. Mean 25-OHD level was  $13.27 \pm 7.11$  ng/ml. Vitamin D deficiency and severe VD deficiency was found in 36 (51.40%) and 26 (37.10%) respectively. Table 2 shows effects of general variables on VD status. Children younger than 10 years of age were more likely to have VD deficiency (64.4%) compared to children above 10 years of age (30.6%), however this was not statistically significant (p-value 0.346). Similarly, boys were more likely to have VD deficiency (77.8%) compared to girls (22.2%). This is also not significant (p-value 0.070).

Children with BMI  $\leq 18.5$ kg/m<sup>2</sup> were more likely to have VD deficiency (55.6%) as compared to children with BMI  $> 18.5$ kg/m<sup>2</sup> (44.4%), but this is not significant (p-value 0.396).



**Figure 1:** Vitamin D status in children with Steroid Sensitive Nephrotic Syndrome

Children younger than 6 years were more likely to have VD deficiency (69.4%) compared to children above 6 years of duration of symptoms (30.6%) (p-value 0.842). There was no effect of disease duration on Vitamin D status since majority of study participants has disease duration less than 6 years compared to children with disease duration more than 6 years.

Variables		Vitamin D Status				p-value*
		Sufficiency N (%)	Insufficiency N (%)	Deficiency N (%)	Severe Deficiency N (%)	
Age group	≤10 yrs n=42	1 (33.3)	3 (60)	25 (69.4)	13 (50)	0.346
	>10 yrs n=28	2 (66.7)	2 (40)	11 (30.6)	13 (50)	
Gender	Male n=47	3 (100)	2 (40)	28 (77.8)	14 (53.8)	0.070
	Female n=23	0 (0)	3 (60)	8 (22.2)	12 (46.2)	
BMI	≤18.5 kg/m <sup>2</sup> n=37	1 (33.3)	1 (20)	20 (55.6)	15 (57.7)	0.396
	>18.5 kg/m <sup>2</sup> n=33	2 (66.7)	4 (80)	16 (44.4)	11 (42.3)	
Disease duration	≤6 yrs n=47	2 (66.7)	4 (80)	25 (69.4)	16 (61.5)	0.842
	>6 yrs n=23	1 (33.3)	1 (20)	11 (30.6)	10 (38.5)	

**Table 2:** Correlation of Vitamin D Status with general variables of study participants (n=70)

\*Chi-square test, BMI: Body Mass Index

## **DISCUSSION**

With increasing awareness regarding vitamin D deficiency globally, many studies have documented varying degrees vitamin D deficiency/insufficiency in paediatric population including children with nephrotic syndrome.<sup>6-9</sup>

Current study is first study on VD status in children with steroid sensitive nephrotic syndrome. This study has highlighted that overall more than 95.71 % of study participants had suboptimal VD status with mean VD level < 13.27ng/ml. This is consistent with a general view of VD status in other than nephrotic populations in both local and international evidence.<sup>7,10-12</sup>

There was VD deficiency in more than half (51.40%) of study population, and severe VD deficiency was found in more than 37.10% cases. This could be due to overall low VD levels in all age groups with various conditions as evident in literature or could be an effect of corticosteroid therapy.<sup>21,22</sup> There is no common practice of VD supplementation to all children with SSNS on steroid therapy at our centre. Also, we have excluded all those children who were already taking VD supplementation. Thus, it reflects the overall picture of either lack of dietary intake or sunlight light exposure, a more physiological explanation.<sup>5,10,20</sup>

Consistent with our findings Weng et al showed in a study on vitamin D status in children with SSNS, that VD insufficiency in 68.3%, VD deficiency in 19.5%.<sup>13</sup> Weng et al showed VD sufficiency in 9.8% like our finding of 4.3%.<sup>13</sup> Moreover, mean 25-OH level(13.27ng/ml) in our study is also like 16.4 ng/ml as shown by Weng et al.<sup>13</sup> A higher frequency of VD deficiency (77.8%) and severe VD deficiency (53.8%) in boys compared to girls (22.2 & 46.2%) may reflect overall male to female ratio in study population.

In this study, high frequency of VD deficiency (69.4%) in younger children compared to older children (30.6%) could be due to lack of sun exposure or lack of dietary intake in younger age group since this age group is more vulnerable to malnutrition and micronutrient deficiencies. This contrasts with study by Weng et al for USA, who observed higher VD deficiency in older age group.<sup>13</sup> This difference may be due to seasonal variation and availability of sunlight in winter is less than summer in addition to geographical variation.<sup>23,24</sup>

Though slightly higher frequency of VDD and severe VD deficiency in children with low BMI (18.5 kg m<sup>2</sup>) compared to children with high BMI is unexplained since we know that children with high BMI/ obesity are more at risk of suboptimal vitamin D levels.<sup>19,23,24</sup>

We found no effects of disease duration on VD status which is also unexplained since we expect that children with long duration are more exposed to steroid and more likely to result in suboptimal levels.<sup>14-16</sup>

### **Limitations:**

Dietary intake of vitamin D, duration of sunlight exposure, bone biochemistry, cumulative dose of steroids consumed by patients are the major factors which may influence the vitamin D status. We have not compared the VD status in relation of steroid use as VD status may vary with cumulative dose of steroid.

### **Conclusion:**

Our findings of suboptimal VD status in 95.71% of children with SSNS are consistent with VD status in children with various disorders other than SSNS. Majority of children were either VD deficient or severely deficient. We recommend that, 25-OH levels should be measured in all children with SSNS. VD supplementation in recommended daily allowances may be carried in all children with SSNS who require repeated doses of steroid for maintenance of remission. We recommend further studies to determine the correlation of steroid use, vitamin D status, disease activity (relapse state/remission) and response to VD supplementation.

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