Original Research Article

A study on vitamin d status in children with nephrotic syndrome

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Abstract

Background& objectives: Children with idiopathic nephrotic syndrome (NS) often exhibit abnormal Vitamin D metabolism despite preserved renal function. Serum concentrations of 25-hydroxyvitamin D [calcidiol or 25(OH)D], the best marker of body vitamin D stores may be decreased in children with NS. In NS, suboptimal 25(OH)D concentrations may lead to secondary hyperparathyroidism and metabolic bone disease, notably osteomalacia. Hence our study is an attempt to measure 25(OH)D levels in children with nephrotic syndrome during relapse and remission. **Methods:** This case control study was conducted in the hospitals attached to Kamineni Institute of Medical Sciences, between November 2017 to May 2019. This study included 30 children with nephrotic syndrome aged between 1 & 14 years. Blood sample was collected for estimation of serum 25(OH)D, albumin, calcium, phosphorus, alkaline phosphatase and creatinine, twice, once in relapse and once in remission. In control group of 30 children same set of investigations were done only once. **Results:** In all the cases serum concentration of Vitamin D was reduced significantly during relapse (mean=12.09 ng/ml) and slightly improved during remission (mean=17.07 ng/ml). There was significant variation in serum calcium levels when relapse levels (mean=8.68 mg/dl) were compared with remission levels (mean=8.93 mg/dl). Serum albumin was low in all the cases during relapse (mean=3.05 g /dl) and normalised during remission (mean=4.01 g/dl). Levels of Serum Phosphate and Serum ALP did not shown significant variation both during relapse and remission when compared with controls. **Interpretation & conclusion:** Our study showed that there is deficiency of Vitamin D levels in cases of NS both during relapse and remission. Hence, we recommend that Vitamin D and Calcium be supplemented during the course of illness and also continued till their levels return to normal. We recommend prospective large scale multi-centric studies regarding the rationale of treatment of NSchildren with Vitamin D supplementation.

Key words: Vitamin D; Nephrotic Syndrome; Relapse; Remission.

Introduction

Children with idiopathic nephrotic syndrome (NS) often exhibit abnormal Vitamin D metabolism despite preserved renal function[1]. Serum concentration of 1,25-dihydroxyvitamin D [calcitriol or $1,25(OH)_2$ D], the active metabolite of vitamin D is decreased[2,3] or in the normal range[4,5,6]. More importantly, serum concentrations of 25-hydroxyvitamin D [calcidiol or 25(OH)D], the best marker of body vitamin D stores and overall vitamin D nutritional status,[7] is decreased in children with NS[2,3,4,5,6]. These low 25(OH)D concentrations stem from urinary excretion of vitamin D- binding protein, the carrier protein for 25(OH)D[8]. In NS, suboptimal 25(OH)D concentrations may lead to secondary hyperparathyroidism[9] and metabolic bone disease, notably osteomalacia[10,11,12]. A recent case series reported altered bone histology in eight children with NS with normal glomerular filtration rate (GFR), five of whom had serum 25(OH)D less than 30 ng/ml[13]. Most studies of NS have examined vitamin D metabolism during periods of heavy proteinuria,[2,3,4] but children with NS typically respond quickly and completely to high-dose glucocorticoids[14].

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As a result, children with steroid-sensitive nephrotic syndrome(SSNS) are only intermittently proteinuric, during either their first attack or their relapses. During remissions, serum 25(OH)D concentrations are higher than the 25(OH)D concentrations during relapses[5] and are reportedly comparable to the levels in healthy children[6]. Consequently, concern regarding vitamin D nutritional status in childhood NS has focused upon treatment-resistant NS, with its long-standing proteinuria, rather than upon SSNS[15].

Current guidelines from the National Kidney Foundation (NKF) concerning bone metabolism are lacking regarding the measurement of 25(OH)D in persons with NS with normal GFR[16]. In persons with elevated parathyroid hormone (PTH) levels and GFR below 60 ml/min per 1.73 m^2, however, the NKF recommends routine measurement of serum 25(OH) D and supplementation with ergocalciferol (vitamin D2) when serum 25(OH) D is less than 30 ng/ml[16]. Before children with NS can be considered candidates for routine 25(OH) D screening, the prevalence of suboptimal 25(OH) D concentrations in this population should be ascertained.

Aims & Objectives

- To measure 25(OH) D levels in children with nephrotic syndrome during relapse and remission.
- To study whether nephrotic syndrome patients have vitamin D deficiencycompared to controls.
- To compare vitamin D status in different subgroups of nephrotic syndrome to evaluate whether clinical course of nephrotic syndrome affect vitamin D status.

Materials and methods

Source of data

Patients diagnosed to have nephrotic syndrome aged between 1 and 14 years attending paediatric outpatient department or admitted in the wards of hospitals affiliated with Kamineni Institute of Medical

Sciences, Hyderabad.

Method of collection of data (including Sampling Procedures if any)

Children with nephrotic syndrome of either sex aged between 1 and 14 years attending paediatric OPD or admitted in wards of both the hospitals attached Kamineni Institute of Medical Sciences during one and half year period (November 2017 to May 2019) were recruited in the study.

All the necessary clinical details were collected as per the proforma. Each subject enrolled in the study was examined in detail.

Type of the study

Case control study.

Inclusion Criteria

- Patients satisfying clinical and biochemical criteria of nephrotic syndrome ofeither sex between 1 and 14 years of age.
- Only children with normal GFR value (as measured by Schwartz formula*).
- All types of nephrotic syndrome –First episode NS.

Infrequent relapses.

Frequent relapses.

Steroid dependence.

Steroid resistance.

*Schwartz Formula: GFR (ml/min/1.73 m^2) = k x height (cm)/ Serum creatinine(mg/dl)

The value of K as originally proposed by Schwartz is 0.34 in preterm infants, 0.45 in term infants, 0.55 in children and adolescent girls and 0.7 in adolescent males.

Exclusion Criteria

- Patients suffering from other chronic illness.
- Patients with evidence of chronic kidney disease and acute kidney injury.
- Patients treated with medicines known to alter vitamin D metabolism
- Those patients who refuse to be included in the study.

Sample size and Study Design

- 40 children with nephrotic syndrome were enrolled in the study.
- A control group of 40 children matched for age and gender were selected fromthe immunization clinic in the same hospital.

Method of Examination

Purpose of the study was explained to the parents and a pre-structured proforma was used to record the relevant information from the subject enrolled in the study.

Informed consent was taken from the parents or guardian.

Measurement of Serum Vitamin D Levels

25(OH)D was measured in venous blood by chemilumescence method.

Duration of study

18 Months

Results

Table -1 : Age distribution of cases and controls

Age Group	Test Subjects		Controls	
	No. of Subjects	Percentage	No. of Controls	Percentage
1-6 Yrs	30	75	32	80
7-14 Yrs	10	25	8	20
Total	**40**	**100**	**40**	**100**

This study included 80 children in total out of which 40 were test subjects and 40 were controls. Children from 1 yr to 14 yrs were included and grouped in to 1-6 yrs group and 7-14 yrs group.

There were 30 test subjects (75%) and 32 controls (80%) in the 1-6 yrs groups while 7-14 yrs group had 10 tests (25%) and 8 (20%) controls.

Table -2 : Sex distribution of cases and controls

Sex	Test Subjects		Controls		TotalCases	Total Percentage
	No. of Subjects	Percentage	No. of Controls	Percentage		
Male	25	62.5	30	75	55	68.75
Female	15	37.5	10	25	25	31.25
Total	**40**	**100**	**40**	**100**	**80**	**100**

Among test subjects 25 were male children and 15 female children while there were 30 males and 10 females in the controls. In total, 55 were males and 25 females.

Table - 3 : Clinical profile of children with NS

Clinical profile	Number of Cases	Percentage
First Episode	15	37.5
Frequent Relapser	5	12.5
Infrequent Relapser	12	30
SDNS	6	15
SRNS	4	10

Laboratory Parameters

The blood levels of Calcium, Phosphate, Albumin, ALP and Vitamin D were analysed in all cases, once during relapse and once during remission in test subjects and once for controls.

The mean, median and standard deviation were calculated. *P* values were calculated for validation of the data statistically through the T- Test. They are represented and explained in the corresponding sections below.

Table - 4 : Comparison of Serum Calcium (mg/dl) in NS and controls

Serum Calcium		Mean	Median	Std. Deviation
Test Subjects	Relapse	8.68	8.7	0.55
	Remission	8.93	8.85	0.33
Controls		8.82	8.8	0.37

Mean sr. calcium levels during relapse were 8.68 mg/dl and during remission were 8.93 mg/dl and that of controls were 8.82 mg/dl. T test analysis showed significant variation during relapse and remission and but no significant change during remission among subjects when compared with controls.
However Median levels didn't vary much among the three groups.

Table - 5 : Comparison of Serum Phosphate (mg/dl) in NS and Controls

Serum Phosphate		Mean	Median	Std. Deviation
Test Subjects	Relapse	5.42	4.2	0.48
	Remission	5.42	4.3	0.21
Controls		5.4	4.3	0.33

The mean levels of phosphate were 5.42 mg/dl, 5.42 mg/dl and 5.4 mg/dl in relapse, remission and controls respectively and T-Test showed no statistically significant variance among them as seen in the table. The Median levels followed the same trend.

Table - 6: Comparison of Serum Albumin (g/dl) in NS and controls

Serum Albimun		Mean	Median	Std. Deviation
Test Subjects	Relapse	3.05	1.9	0.60
	Remission	4.01	2.9	0.40
Controls		3.81	3.9	0.50

Mean sr. albumin levels during relapse were 3.05 g/dl and improved to 4.01 g/dl during remission but still remained under the normal range while in controlsmean levels were 3.81 g/dl.
T-Test showed *p* values comparing all three groups well under the 0.05 value showing strong statistical validation of the improvement during the course of NS.

Table - 7: Comparison of Serum ALP (U/L) in NS and Controls

Serum ALP		Mean	Median	Std. Deviation
Test Subjects	Relapse	124.50	122.00	6.15
	Remission	125.80	124.60	7.16
Controls		123.68	122.50	7.05

The levels of Sr. ALP whose mean for relapse, remission and controls were 124.5 U/L, 125.8 U/L, 123.6 U/L, respectively and T-Test showed no significantvariation among the three groups.

Table - 8: Comparison of Serum Vitamin D (ng/ml) in NS and Controls

Serum Vitamin D		Mean	Median	Std. Deviation
Test Subjects	Relapse	12.09	9.6	5.42
	Remission	17.07	16.2	5.93
Controls		25.90	24.13	3.69

The levels of Sr. Vitamin D showed both observable as well as statisticalvariation during the study.
The mean levels during relapse were12.09 ng/ml, during remission were 17.07 ng/ml and for controls were 25.9 ng/ml. Corresponding p values were all well under the 0.05 mark.
As we analyse the above set of data, the levels of phosphate and ALP do not show much variation in relapse, remission and controls while the levels of Vitamin D,albumin and calcium showed significant observable variation as they show an increasing trend from relapse to remission.

Discussion

The present study was conducted in the department of paediatrics Kamineni Institute of Medical Sciences from November 2017 to May 2019.This study comprised of 40 children with nephrotic syndrome aged between 1and 14 years and 40 age and sex matched controls. 76.6% of children with NS were below six years of age. Male: Female ratio was 3:2. 40% of test subjects were infrequent relapsers while only 6.6% belonged toSRNS group.
The blood levels of calcium, phosphate, albumin, ALP, Vitamin D, Creatinine were analysed in all test subjects once during relapse and once during remission. For controls all the above lab parameters were done only once.

Serum Calcium

In our study, we observed that there was not much variation in serum calcium levels in Remission phase and control group but there seems to be significant variation when comparing relapse levels with remission levels and controls levels. Mean calcium in relapse and remission was 8.68 mg/dl and 8.93 mg/dl respectively and 8.82 mg/dl in controls.
Study conducted by Banerjee et al[17] in 2013 showed no significant variations in the levels of serum calcium in Nephrotic syndrome group and Control group.

Serum Phosphate

We noted that there was not much variation in serum levels of phosphate as well in the course of study. Mean serum levels of Phosphate in relapse was 5.32 mg/dl and was 5.42 mg/dl in remission and was 5.4 mg/dl in controls. The study by Benarjee et al[17] showed similar observation.
In another study Micheal Freundlich et al[18]. noticed that total serum calcium concentration was slightly lowered and Phosphorous was increased in relapse than in remission.

Serum Albumin

In our study, Serum albumin was low in all cases during relapse with mean levels of 3.05 g/dl and normalised during remission with mean levels of 4.01 g/dl and healthy controls has normal levels with mean value of 3.81 g/dl.

Serum ALP

In our study, serum ALP levels were slightly lower in Nephrotic syndrome group with mean values of 119.3 U/dl and 124.76 U/dl in relapse and remission respectively than in controls who had a mean value of 125.0 U/dl. This was not statistically significant variation. But, study by Benarjee et al[17] revealed that ALP levels were significantly reduced in NS group compared to the controls.

Vitamin D

Serum concentration of Vitamin D in this study, the best marker of Vitamin D stores and overall Vitamin D nutritional status[19] was reduced significantly during relapse with mean levels of 12.09 ng/ml and slightly improved during remission with mean levels of 17.07 ng/ml, but still lower compared to healthycontrols.
These low concentration stems from urinary excretion of 25-Hydroxy Vitamin D[20]. However, the levels were normal in healthy controls with mean levels of 24.9 ng/ml, but still lower compared to healthy

controls.Previous studies estimating 25(OH)D levels in NS remission have reported mixed results.

Early studies by Freundlich et al[21]. and Huang et al[22]. showed that low levels of 25(OH)D during relapse normalized quickly post-remission, after the resolution of proteinuria and loss of DBP by urinary leakage.

In contrast, Bykilli et al[23]. showed that although 25(OH)D levels rise after remission has been achieved with steroid therapy, they are still lower than those in controls at 3 months.

A study by Weng et al[24]. also revealed significantly low levels of 25(OH)D in NS remission compared to controls after a median of 3.5 months from last relapse, but there was no correlation with time interval since last relapse.

In our study except first episode (30%), the remaining test subjects (70%) were on calcium and vitamin D supplementation before enrolling into the study.

The first episode NS children were started on calcium and Vitamin D supplementation along with steroids. All the test subjects including first episoders were on daily prednisolone therapy during the course of study.Banerjee et al observed that ‑Within the NS group, there was no significant difference in the levels of 25(OH)D, PTH, calcium, phosphate, or ALP when patients were segregated by sex, type of NS, current steroid treatment, and other immunosuppressive treatment. 25(OH)D levels also did not differ in 15 patients on calcium and vitamin D supplementation compared to those not on supplements[17].

Conclusion

The following observations were made in the following study,

1. Serum Calcium levels improved from relapse to remission. During relapse, levels were low when compared with controls but not while in remission.
2. Levels of Serum Phosphate and ALP showed no significant variation both during relapse and remission.
3. Levels of Albumin improved from relapse to remission. Levels remained low both during relapse and remission when compared to healthy controls.
4. Vitamin D levels were low in all the cases of nephrotic syndrome both during relapse and remission. Vitamin D levels showed improvement from relapse to remission. But, remained significantly low compared to controls both during relapse and remission.
5. SRNS group had the lowest levels of Vitamin D compared to other groups.
6. Frequent relapsers had lesser improvement in vitamin D levels compared to other groups.
7. First episoders showed the most significant improvement in Vitamin D levels compared to other groups (showing near normal mean levels).

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