Original Article

Prevalence of Vitamin D3 deficiency among pediatric patients with idiopathic nephrotic syndrome in remission - A cross-sectional observational study from Vadodara, Gujarat

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ABSTRACT

Background: Vitamin D deficiency occurs in nephrotic syndrome (NS) through various mechanisms, resulting in loss of both, Vitamin D binding protein and 25-(OH) D, in the urine leading to the risk of bone disorders. **Objectives:** The objectives of the study were to detect the prevalence of Vitamin D deficiency in children with idiopathic NS during remission. **Methods:** This study was conducted from April to November 2016 at the pediatric nephrology clinic at a tertiary care hospital in Vadodara. A total of 34 children were enrolled with idiopathic NS in remission, of which 14 had first attack of NS and ten of Frequently Relapsing Nephrotic Syndrome (FRNS) and Infrequently Relapsing Nephrotic Syndrome each. Vitamin D levels were measured using serum levels of 25-(OH) D by chemiluminescence method. **Results:** Vitamin D deficiency was observed in 28 of 34 (82%) children; of which, 16 (47%) had severe deficiency and 12 (35.2%) had mild to moderate deficiency. Children with the first attack of NS had a median Vitamin D level of 8.17 ng/ml (interquartile range [IQR] 2.9–28), IFRNS had a median of 6.8 ng/ml (IQR 2.9–33), and FRNS had the lowest median of 5.3 ng/ml (IQR 2.9–16). Although there were differences among all the 3 groups, differences were not statistically significant (Kruskal–Wallis 4.89, p=0.08) which showed decreased levels of Vitamin D. **Conclusion:** High prevalence of Vitamin D deficiency was observed in all 3 groups of idiopathic NS; the lowest being in FRNS. There was no significant association with lower levels of Vitamin D and relapses in NS. More research is needed to assess Vitamin D deficiency and to ensure the effect of Vitamin D supplementation for children with NS.

Key words: Deficiency, Pediatric Nephrotic syndrome, Remission, Vitamin D

Nephrotic syndrome (NS) is a common disorder of childhood (common in the age group of 2–8 years) which results in proteinuria and hypoproteinemia. NS remains the most common manifestation of glomerular disease in childhood [1]. Global incidence of NS is reported to be 20–40 per million populations; whereas in the Indian subcontinent, it is estimated to be 90–100 per million populations [1]. Minimal change nephropathy is the most common cause of NS in children. Hypotheses on the pathogenesis of the syndrome have evolved from the concepts of "immune dysregulation," "increased glomerular permeability," and "podocytopathy" [1–4].

Clinically, NS is categorized into the first attack of NS, infrequently relapsing nephrotic syndrome (IFRNS) and frequently relapsing nephrotic syndrome (FRNS) on the basis of number of relapses in past 6–12 months of the disease [3]. The major cause of Vitamin D deficiency in children with NS is due to loss of both, Vitamin D binding protein and 25-Hydroxyvitamin D (25-(OH) D) in the urine, secondary to proteinuria. Vitamin D deficiency in India is further aggravated by nutritional factors, sunlight (increased melanin pigment preventing absorption), and cultural influences [5]. Deficiency in 25(OH) D may lead to hypocalcemia, hyperparathyroidism, and diminished bone mineral density/content [3].

When the 25(OH) D is low, plasma calcium is maintained by increased osteoclastic activity, reducing the mineral content of the bones. Complicating impact of Vitamin D deficiency on the bones in children with NS is the repeated exposure to glucocorticoids [1]. In studies of pediatric patients with primary or secondary NS, 25 (OH) Vitamin D deficiency ranges from 20–100% in patients surveyed at various stages of the disease [6–10]. It is possible that the low value of 25(OH)D results in low blood levels of other Vitamin D metabolites, such as [1,25-(OH)2D] and 24,25-(OH)2D; a deficiency of these compounds may cause defective intestinal absorption of calcium (alpha) and resistance to the calcemic action of parathyroid hormone (PTH), resulting in hypocalcemia [11].

Children with NS and adult survivors of steroid-sensitive minimal change disease have shown decreased bone

mineralization and bone abnormalities. These findings have led to an increased interest in supplementation of calcium and Vitamin D in children with NS [9,12]. To the best of our knowledge, a single study from India (Kolkata) in this context has been conducted so far, wherein Vitamin D stores were found to be low 3 months after NS relapse but showed an increase with longer remission time. The levels were not influenced by disease characteristics or therapy. The effect of low 25(OH) D levels on the disease course in patients with NS needs to be evaluated [13]. Hence, we conducted this study to determine the prevalence of Vitamin D deficiency among children with idiopathic NS during the remission phase.

MATERIALS AND METHODS

A cross-sectional observational study was conducted in children attending pediatric nephrology clinic in department of pediatrics at tertiary care hospital in Vadodara from April 2016 to November 2016. The study was approved by Scientific Review Committee and Institutional Ethics Committee on Human Research of the hospital. All cases of NS either newly detected or in remission phase were enrolled in the study. All children in the age group of 2 years–12 years with NS of duration 1 month at the time of remission and not more than 3 months were included. Patients treated with Vitamin D supplements or medications which are known to cause Vitamin D deficiencies or affect its metabolism and children with secondary causes of NS, for example, SLE, malaria, drugs, and others were excluded.

All the children had received prednisolone (2 mg/kg) daily as a gold standard treatment. In the first attack, prednisolone is given in the dose of 2 mg/kg for 6 weeks followed by 1.5 mg/kg for 6 weeks and then gradually tapered. For infrequent relapses, prednisolone 2 mg/kg is given daily until remission, followed by 1.5 mg/kg on alternate days for 4 weeks. In children with FRNS, prednisolone was given 2 mg/kg daily until remission, followed by 1.5 mg/kg on alternate days for 4 weeks followed by 0.5–0.75 mg/kg on alternate days for 9–18 months.

To confirm the remission status of child, spot urine albumin test was performed using sulfosalicylic acid test on the urine sample collected during the visit [14]. Child having trace or nil urine albumins on two consecutive visits 1 week apart were taken to be in remission. After taking informed written consent, blood sample was collected in plain Vacutainer and sent for estimation of serum Vitamin 25(HO)D levels by chemiluminescence method [15]. Vitamin D deficiency was categorized as 25 (OH) D levels <20ng/ml. It was further categorized as insufficiency (16–20 ng ml), moderate deficiency (5–15 ng/ml), and severe deficiency (<5 ng ml). No, follow-up samples were taken.

The obtained data were entered into MS Office Excel in a password protected file, and the same was analyzed using MedcalC version 12.5.0.0 (Trial version). Data being non-normally distributed, Vitamin D levels were reported in the form of median and. Statistical analysis was done to see the difference in Vitamin D levels across the NS, FRNS, and IFRNS groups using Kruskal–Wallis test. p-value of 0.05 was considered statistically significant.

RESULTS

During the study period, 34 patients were enrolled; of which, 19 were males (55.9%) and 15 females (44.1%). The mean age was 5.7±2.7 years (95% confidence interval: 4.79–6.68), and the range was 2–12 years. Vitamin D deficiency was seen in 28 of 34 patients (82%). 16 patients (47%) had severe deficiency, seven (20%) had mild to moderate deficiency, and five (14.7%) had insufficient levels of Vitamin D. Normal levels of Vitamin D were seen in only 6 (14%) patients (Table 1). There was no significant difference in Vitamin D levels among the males and females (p=0.89).

Among the 34 children included in the study, 14 had first attack of NS while 10 each had FRNS and IFRNS. There was no significant difference in the Vitamin D deficiency among subtypes of the NS (Chi-square 0.769, p=0.68). Median (interquartile range [IQR]) days of remission were 41 days (range 30–59 days). There was no significant correlation between age and Vitamin D levels (p=0.58) or days of remission and Vitamin D levels (p=0.34).

Children with first attack of NS had a median (IQR) Vitamin D level of 8.17 (2.9–28) ng/ml, those with IFRNS had a median (IQR) Vitamin D level of 6.8 (2.9–33) ng/ml, while children with FRNS had the lowest median (IQR) Vitamin D level of 5.3 (2.9–16) ng/ml (Fig. 1). Although all the three groups showed decreased levels of Vitamin D, Kruskal–Wallis one-way analysis of variance did not show any statistically significant difference in the Vitamin D levels across the three groups (Kruskal–Wallis 4.89 p=0.08).

DISCUSSION

Studies with evidence on the prevalence of Vitamin D deficiency and its relation to NS are only a few [12]. To the best of our knowledge, only one case–control study has been carried out to explore Vitamin D deficiency in pediatric patients with idiopathic NS in remission in the Indian context [13]. We, therefore, believe that our report may contribute useful additional data to the limited

Table 1: Vitamin D deficiency among the children with nephritic syndrome

Vitamin D level (ng/ml)	First attack (n=14)	FR (n=10)	IFR (n=10)	Total n=34 (%)
<5 (Severe)	6	5	5	16 (47)
5–15 (Moderate)	3	2	2	7 (20.5)
16–20 (Insufficiency)	1	3	1	5 (14.7)
More than 21 (Adequate)	4	0	2	6 (17.64)

Chi-square is 0.769, DF=2, P=0.68

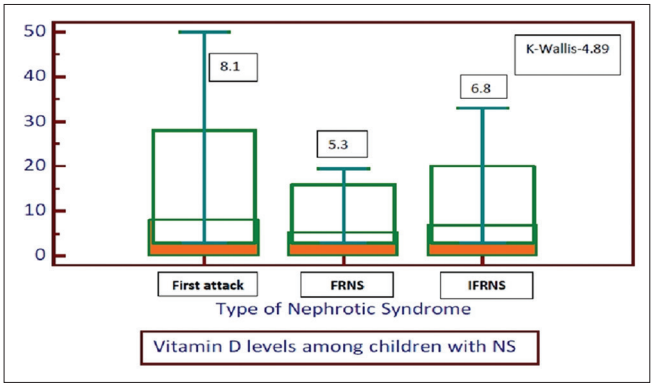

Figure 1: Median vitamin D (mg/l) among children with nephrotic syndrome, frequently and infrequently NS attending pediatric nephrology clinic and wards in tertiary care hospital of Vadodara, Gujarat

available evidence base. The specific role of Vitamin D in NS should be identified so that an effective and early treatment modality can be achieved [14]. This study showed a high prevalence of Vitamin D deficiency, with 82% NS patients having 25 (OH) D levels of <20 ng/ml which is higher than the study by Banerjee *et al.*[13].

Almost half of the pediatric patients in this study group had severe Vitamin D deficiency; this was almost equally distributed among the first attack, FRNS, and IFRNS patients. A case–control study by Banerjee *et al*. showed a positive correlation with months elapsed since last NS relapse (r s=+0.4, p=0.012) [13]. However, this was not the case in our study group. A small sample size could be one of the reasons for these findings, which, however, could be validated by a follow-up the study of the same patient cohort.

In another study done by Nielsen *et al*. at Denmark, 13 of the 14 children (prospective study) with the first episode of NS before treatment with glucocorticoids had 25(OH) D deficiency including 12 (86%), who had moderate or severe Vitamin D deficiency [16]. However, a very small sample size would make it difficult to compare the Vitamin D deficiency levels across the different groups.

Median Vitamin D levels in the study by Banerjee *et al*. were lower in NS patients with remission period <3 months but similar to that of controls in patients in remission for >3 months (median 14.23 [interquartile range 12.19–17.63] vs. 19.75 [14.04–28.38] ng/ml, respectively; p=0.039) [13]. In our study, the median levels of Vitamin D for patients with the first attack of NS were higher than FRNS and IFRNS, though not statistically significant. Biochemical parameters such as serum calcium, PTH, and phosphorus levels could not be assessed, which was the limitation of this study.

This study can be taken forward as a prospective study with monitoring of Vitamin D levels three monthly. Furthermore, a case–control study with and without Vitamin D supplementation to study the effect of the same in these patients, so as to set up departmental policy can be undertaken. After this study, we have started supplementing all the children with NS with 400–600 IU per day Vitamin D along with calcium. We recommend more multicenter case–control studies with larger sample size with longer follow-up to make an ideal protocol for estimation and supplementation of Vitamin D in idiopathic NS to prevent bone diseases in adolescent and childhood NS survivor.

CONCLUSION

Decreased Vitamin D levels were observed in all the three groups, i.e. first attack NS, FRNS, and IFRNS of our study population, lowest being in the children with frequent relapses of NS. An ideal protocol can be made where the estimation of Vitamin D is done before starting steroid treatment for NS and supplementation of Vitamin D started at the earliest while assessing the deficiency during the course of the disease and remission.

REFERENCES

1. Nelson Textbook of Pediatrics. Available from: http://www.NLMCatalog-NCBI. [Last cited on 2016 Dec 18].
2. Leroy S, Guigonis V, Bruckner D, Emal-Aglae V, Deschênes G, Bensman A, *et al.* Successful Anti-TNFα treatment in a child with posttransplant recurrent focal segmental glomerulosclerosis. Am J Transplant 2009;9:858-61.
3. Srivastava RN. Pediatric Nephrology. New Delhi: JP Medical Ltd; 2011. p. 570.
4. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res 2005;122:13-28.
5. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, *et al.* Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med 2010;152:307.
6. Freundlich M, Bourgoignie JJ, Zilleruelo G, Jacob AI, Canterbury JM, Strauss J. Bone modulating factors in nephrotic children with normal glomerular filtration rate. Pediatrics 1985;76:280-5.
7. Freundlich M, Bourgoignie JJ, Zilleruelo G, Abitbol C, Canterbury JM, Strauss J. Calcium and vitamin D metabolism in children with nephrotic syndrome. J Pediatr 1986;108:383-7.
8. Selewski DT, Chen A, Shatat IF, Pais P, Greenbaum LA, Geier P, *et al.* Vitamin D in incident nephrotic syndrome: A Midwest pediatric nephrology consortium study. Pediatr Nephrol 2016;31:465-72.
9. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
10. El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, *et al.* Effect of vitamin D replacement on musculoskeletal parameters in school children: A randomized controlled trial. J Clin Endocrinol Metab 2006;91:405-12.
11. Gupta P. PG Textbook of Pediatrics. 1st ed., Vol. 3. New Delhi: Jaypee Brothers Medical Publishers Private Limited.; 2015. p. 3038.
12. Romagnoli E, Pepe J, Piemonte S, Cipriani C, Minisola S. Management of endocrine disease: value and limitations of assessing vitamin D nutritional status and advised levels of vitamin D supplementation. Eur J Endocrinol 2013;169:59-69.
13. Banerjee S, Basu S, Sengupta J. Vitamin D in nephrotic syndrome remission: A case–control study. Pediatr Nephrol 2013;28:1983-9.
14. Fine LG, Salehmoghaddam S. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Ch. 192. Atlanta, Georgia: Butterworth Publishers, a division of Reed Publishing; 1990.
15. Siemens Healthcare Diagnostic. Vitamin D Total (vitD). Tarrytown, NY, USA: Siemens Healthcare Diagnostic; 2014. p. 1-18.
16. Nielsen CA, Jensen JE, Cortes D. Vitamin D status is insufficient in the majority of children at diagnosis of nephrotic syndrome. Dan Med J 2015;62:1-2.

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