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Original Article

Vitamin D and Calcium Levels in Children With Nephrotic Syndrome, Surveillance in a Tertiary Medical Center

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ABSTRACT

Background and Aim: The incidence rate of nephrotic syndrome (NS) is 2-7 children per 100,000 children. Children with NS usually have some calcium homeostasis problems leading to abnormal bone histology, hypocalcemia, reduced serum vitamin D metabolites, and impaired intestinal absorption of calcium during their disease or following treatment.

Methods: This is a prospective study on patients with NS on their first visit before any initial treatment. One hundred and three children aged 2-12 years referring to our nephrology department from March 2018 to June 2019 were enrolled in this study. Serum concentrations of calcium, phosphorus, albumin, 25(OH)2 vitamin D3, and creatinine were measured in all patients. The correlation of 25(OH) vitamin D3 with the type of nephrotic syndrome, gender, and age of the patients was evaluated.

Results: Sixty-two patients were male (60.2%) and 41 cases were female (39.8%). Vitamin D deficiency (<20 ng/dL) was observed in 87 out of 103 patients (96.7%). Also, 24 patients underwent kidney biopsy: ten patients were found with minimal change disease (41.7%), seven patients (29.2%) showed focal segmental glomerulosclerosis, and seven cases had diffuse mesangial proliferation. Mean serum levels of calcium, phosphorous, albumin, and cholesterol were 7.512, 4.756, 1.932, and 450.68 mg/dL, respectively, and there was no correlation between vitamin D levels and these parameters except albumin.

Conclusion: Because of the high prevalence of vitamin D deficiency and its serious consequences in NS patients, it is recommended to measure the levels of this vitamin at the first visit and treat this deficiency, if necessary, along with other specific treatments.

Keywords: Calcium metabolism, Minimal change disease, Nephrotic syndrome, Vitamin D deficiency

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Introduction

In children up to the age of 16 years, the most frequent glomerular disease is idiopathic nephrotic syndrome (NS with three forms, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and diffuse mesangial proliferation (DMP) [1]. The most common type of NS is MCD, which is its most sensitive type to corticosteroids. NS involves 2-7 cases in every 10,000 children each year and 90% of these patients are categorized into the idiopathic NS group and approximately 80-90% of children respond to steroid therapy in the first three weeks of treatment [2]. NS children often display some calcium homeostasis disturbances leading to abnormal bone histology, including hypocalcemia, reduced serum vitamin D metabolites, impaired intestinal absorption of calcium, and elevated levels of immunoreactive parathyroid hormone (PTH). These are mainly attributed to the loss of some plasma proteins and minerals in the urine as well as steroid therapy consequences [3]. Serum phosphorus concentration usually remains in the normal range. Vitamin D plays an important role in a large number of physiological functions. Its deficiency is associated with many disorders, including calcium and phosphate disturbances, autoimmune diseases, some malignancies, type 2 diabetes mellitus, and susceptibility to infectious diseases and cardiovascular problems [4-6]. Vitamin D is totally inactive biologically and its activation needs enzymatic conversion in some organs, like the kidneys and liver [4]. Vitamin D has a crucial role in the homeostasis of calcium and prevents the occurrence of osteo-malacia or rickets. In the general population, vitamin D supplementation is generally done to obtain other health effects [5]. All forms of vitamin D are not vitamins and behave more like hormones and carry out several essential biological functions through endocrine, paracrine, and intracrine mechanisms [7]. Cholecalciferol is converted to calcidiol in the liver and then to calcitriol in the kidneys [8]. In NS, ionized calcium and an active form of vitamin D are continuously excreted in urine leading to long-term bone problems. Also, corticosteroid therapy may decrease or accelerate bone mass density [9]. Some studies have demonstrated that vitamin D supplements may prevent losing bone density and vitamin D deficiency complications in these patients [6]. The aim of this study was to assess the prevalence of vitamin D deficiency in children with NS presented to our tertiary center and treat those who need standard vitamin D therapy to prevent the above-mentioned complications.

Materials and Methods

This retrospective cross-sectional study was performed on children 2-12 years old with NS referring to our nephrology department (day clinic or inpatient) as a tertiary hospital center from March 2018 to June 2019. Patients with secondary causes of NS, such as systemic lupus erythematosus and post-infection NS were excluded. A total of 103 children were enrolled and their levels of vitamin D, calcium, albumin, cholesterol, and phosphorus were assessed by one-time blood sampling. Also, data on gender, age at diagnosis, and pathologic type of NS (in cases, for whom biopsy was done) were collected. Vitamin D deficiency was categorized as 25(OH)D levels <20 ng/mL and further classified as mild deficiency (10–20 ng mL) and severe deficiency (<10 ng/mL).

All statistical analyses were done using SPSS software, version 23 and the Office Exchange tool. The data were not normally distributed, and vitamin D levels were reported as median and statistical analysis. The correlation between vitamin D levels and gender, age at diagnosis, type of NS, calcium, albumin, and phosphorus was assessed using independent samples t-test and Pearson correlation coefficient. The $P<0.05$ was considered statistically significant.

Results

One hundred and three patients (2-12 years old) were studied, of whom 62 cases were male (60.2%) and 41 cases were female (39.8%). The mean age of patients was 5.2±3.2 years. Vitamin D deficiency was found in 87 out of 103 patients (96.7%) (Table 1). Seventy-five patients (83.3%) had severe deficiency (<10 ng/dL) and 12 patients (13.3%) had mild vitamin D deficiency (10-20 ng/dL). Sufficient levels of vitamin D were seen in only three (3.3%) patients. There was no significant difference in vitamin D levels between males and females ($P=0.534$), and also, there was no significant correlation between age and vitamin D levels ($P=0.7$). Tables 2 and 3 show the calcium and phosphorus levels of patients. Only 24 patients had kidney biopsy. Ten patients had MCD (41.7%), seven patients had FSGS, and seven cases had DMP (29.2%) (Table 4). There was no significant difference in vitamin D levels between the subtypes of the NS ($P=0.22$).

The mean calcium levels were 7.5±0.8 mg/dL and 95 patients (92.2%) had hypocalcemia (calcium <8.8 mg/dL). The mean levels of phosphorous were 4.76±0.86 mg/dL and 52 patients (51.5%) had hypophosphatemia (phosphorous <4.5 mg/dL) (Table 4). The mean cho-

Table 1. Subjects' serum vitamin D levels

Serum Vitamin D levels (ng/dL)	No. (%)
<10	75(83.3)
10-20	12(12.3)
<20	3(3.3

Table 2. Subjects' serum calcium levels

Serum Calcium (mg/dL)	No. (%)
<8.8	95(92.2)
≥8.8	8(7.8)
Total	103(100)

Table 3. Subjects' serum phosphorus levels

Valid	84
Non-valid	19
Mean	4.76
Median	4.60
Standard deviation	0.86
Variance	0.74

Table 4. Renal pathologic findings of 24 cases with renal biopsy

Renal Biopsy Findings		No.	Validity
Validated	Minimal change disease	10	41.7
	Focal segmental glomerulosclerosis	7	29.2
	Diffuse mesangial proliferation	7	29.2
	Total validated	24	100.0

Table 5. Laboratory data of patients and their mean values

Parameter	Mean±SD
Calcium (mg/dL)	7.51±0.8
Albumin (g/dL)	1.93± 0.41
Phosphorous (mg/dL)	4.76±0.86
Cholesterol (mg/dL)	450.70±165.71

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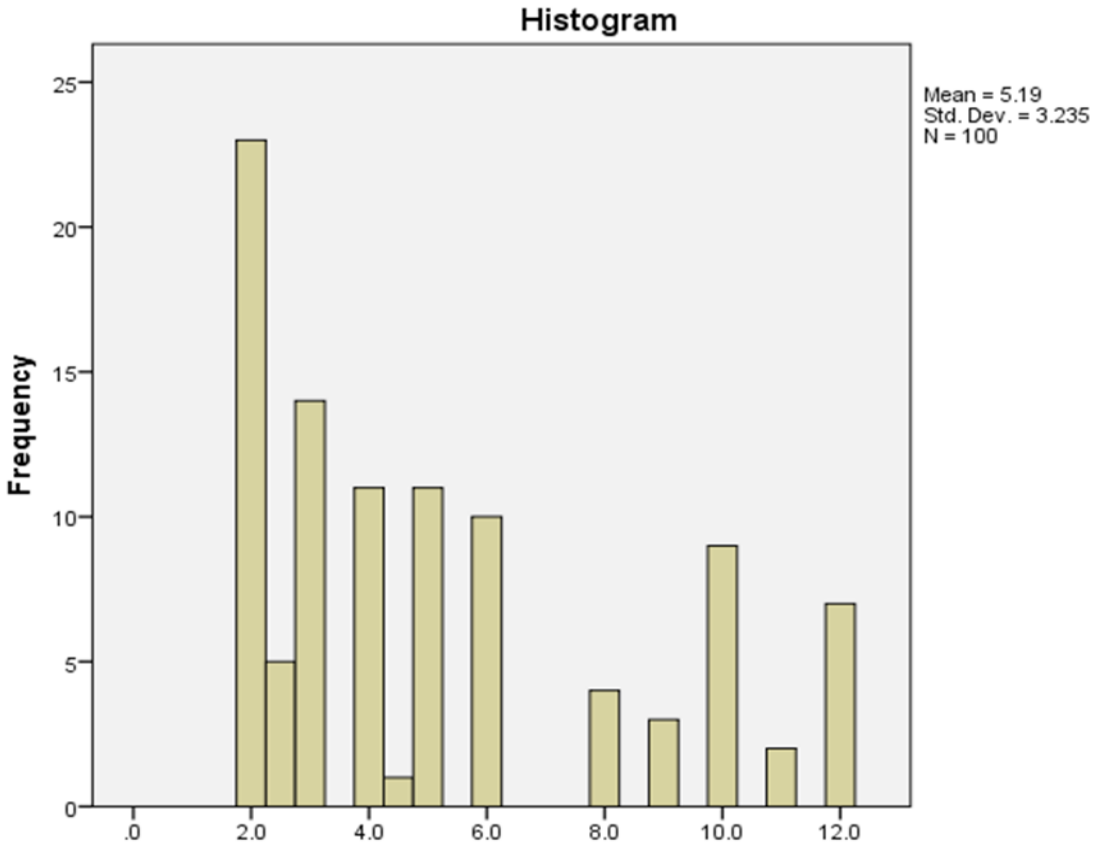

Figure 1. Histogram of frequency of nephrotic syndrome according to age (year)

lesterol levels were 450.68±165.71 mg/dL (Table 5). There was no correlation between the levels of vitamin D and levels of calcium, phosphorous, and cholesterol (P=0.119, P=0.305, and P=0.93, respectively) and the age of the patients. Mean albumin levels were 1.93 ±0.41 mg/dL, and 93 children (90.3% had hypoalbuminemia (albumin <2.5 mg/dL), and ten children had albumin levels of 2.5-2.8 mg/dL that means they had early diagnosis of NS. There was a positive correlation between the average levels of vitamin D and albumin (P=0.404). Figure 1 shows the frequency of NS according to age (years).

Discussion

Low levels of vitamin D have been documented in patients with relapses of NS due to loss of both 25(OH)D and a limited fraction of it in the urine at this time [10]. In a systematic review and meta-analysis done in 2018 by Yousefichaijan et al., the prevalence of vitamin D deficiency (<20 ng/mL) in healthy Iranian children was about 30% with a different pattern in males and females (female: 61% and male: 35%) [11]. We found the prevalence of vitamin D deficiency in children with NS to be about 96.7%, which is much higher than healthy people and there was no difference between males and females in this respect. Marzouk et al. revealed vitamin D deficiency in 96.7% (58/60) of the NS patients and showed a significantly lower 25 hydroxycholecalciferol [25(OH) D] level in nephrotic cases (P<0.001) [12], which is similar to our study.

We had no control group and it was our study limitation. Selewski et al. (2016) demonstrated 100% vitamin D deficiency in 61 NS patients [2]. This study also showed male predominance among the nephrotic group (60.2%). The age of the patients in this study ranged from 3 to 11 years with a median of 9 and a mean of 5.19±3.2347 years. On the contrary, Echeverri et al. showed a lower age at first presentation ranging from seven months to 16 years [13]. In this study, the mean calcium levels were 7.512±0.8181 mg/dL and 95 patients (92.2%) had hypocalcemia (calcium <8.8 mg/dL). The phosphorous mean levels were 4.756±0.8580 mg/dL and 52 patients (51.5%) had hypophosphatemia (phosphorous <4.5 mg/dL). It seems that hypocalcemia and hypophosphatemia in our patients were directly related to vitamin D deficiency. Another cross-sectional study on NS patients

found significantly lower serum calcium, phosphorus , and vitamin D levels in patients with frequent relapses. On the other hand, in patients who had no relapse in the last three months, these items were much nearer to the normal range [9].

Increased blood immunoreactive parathyroid hormone (iPTH) levels have been reported in a few studies [14, 15]. In our study, 24 patients were found with renal biopsy examination. There was no significant difference in vitamin D deficiency between the subtypes of the NS. Mehta and Nanda assessed 30 children diagnosed with NS and divided them into three groups (SSNS, FR/SDNS, and patients in remission). They showed that serum calcium and vitamin D levels were significantly lower in the SDNS group compared to the SSNS group and patients in remission ($P<0.01$) [14]. Gulati et al. showed that vitamin D and calcium supplements improved bone density in children with NS. We could not check this subject in our study as it needs a case-control study of patients with NS who are treated with a group who are treated with vitamin D supplements [16]. We assessed the relationship between phosphorous, cholesterol, and albumin levels and found a positive correlation between vitamin D and serum albumin levels. It means that in patients with higher levels of albumin, serum vitamin D levels are higher than other patients with NS. Aggarwal et al. reported a decrease in serum levels of 25-hydroxyvitamin D [25(OH) D] in adult patients with NS, which could be due to the loss of vitamin D binding proteins in the urine [17]. This result is consistent with our findings. Yang et al. reported that NS patients had low free and total serum calcium low total 25(OH)D and normal total 125(OH)D levels and no PTH response. During the remission of the disease, serum calcium and vitamin D metabolites improved as expected. However, nephrotic patients who achieved complete disease remission continued to have low serum 25(OH)D levels [18].

Conclusion

The levels of vitamin D should be measured at the first visit of children with NS and early treatment of patients with vitamin D deficiency should be considered. In general, assessment of serum vitamin D levels at baseline and at regular intervals is recommended in patients with NS. Preventive administration of calcium and vitamin D with regular follow-up of their serum levels and clinical examination is recommended.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethical Institute of Tehran University of Medical Science. (Code: IR.TUMS.CHMC.RES.1397.096)

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declared no conflict of interest.

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