



Relationship between Serum 25(OH)D Levels and Blood Pressure in Children with Nephrotic Syndrome

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Abstract

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BACKGROUND: Vitamin D plays an eminent role in the renin-angiotensin system that may interfere with blood pressure regulation. Children with nephrotic syndrome (NS) are often observed with low serum vitamin D levels that may lead to Vitamin D deficiency status.

AIM: This study aimed to investigate the correlation between serum vitamin D [25(OH)D] levels and blood pressure in children with NS.

METHODS: A cross-sectional, observational analytic study was conducted in 35 children NS with minimal change diseases from February to August 2019 in Haji Adam Malik General Hospital, Medan. Blood pressure was examined and serum Vitamin D levels along with serum creatinine, albumin, and calcium were measured.

RESULTS: Of 35 children, 21 children (60%) had proteinuria. Regarding the category of Vitamin D status, there were 40% and 34.3% with deficiency and severe deficiency of Vitamin D, respectively. The median serum Vitamin D levels were not significantly different among the age group. Children with proteinuria showed lower serum Vitamin D levels ($P < 0.001$). There was an elevation of systolic and diastolic blood pressure in children with proteinuria ($P = 0.039$ and $P = 0.036$, respectively). Our study showed a weak negative correlation between serum Vitamin D levels and either systolic or diastolic blood pressure ($r = -0.114$ and $r = -0.174$, respectively).

CONCLUSION: Both Vitamin D deficiency and severe deficiency are common in children with NS. In this study, serum Vitamin D levels have been shown to have a weak negative correlation with blood pressure in children with NS.

Introduction

Nephrotic syndrome (NS) is one of the most common kidney disorders in children. The incidence of NS in children in the United States of America and the United Kingdom is 2–7 newly diagnosed cases per 100,000 children annually, with a prevalence of 12–16 cases per 100,000 children [1], [2]. Incidence of NS is higher in developing countries. In Indonesia, it is reported that 6 per 100,000 children annually, aged <14 years old, with boy compared to the girl is 2: 1 [3].

Complications of NS are divided into two main entities, which are complications related to the disease and complications related to therapy. Complications related to the disease compose of infections (peritonitis, sepsis, and cellulitis), thromboembolic (vein thromboembolic and pulmonary emboli), hypovolemic crisis (abdominal pain, tachycardia, and hypotension), cardiovascular disorders (hyperlipidemia), renal failure, and others like hypothyroid, and hypocalcemia. One of the etiologies of hypocalcemia is related to Vitamin D metabolism abnormality [1].

Studies in the United States, Canada, and Europe showed that 20–100% of the geriatric population

suffers from Vitamin D deficiency and approximately 1 billion population all over the world has either Vitamin D deficiency or insufficiency [4]. Southeast Asian Nutrition Surveys (SEANUT) in Indonesia, Malaysia, Thailand, and Vietnam in 2016 showed in Indonesia, only 5% of children with an adequate 25(OH)D levels (serum levels >30 ng/mL) [5].

A previous study showed that 93% of children with NS have Vitamin D deficiency, while 86% with moderate to severe levels of severity [6]. One active form of Vitamin D, calcitriol, is known as an important factor in regulating the angiotensin-renin system which plays an important role in hypertension. Therefore, normal levels of calcitriol not only benefit in maintaining calcium homeostasis but also electrolytes, hormonal, and blood pressure homeostasis [7].

A study in mice reported that Vitamin D significantly suppresses the renin expression gene through the binding process of transcription factor cAMP response element-binding protein (CREB) hence suppress the mechanism of action CREB in the renin promoter gene [8]. As far as our concern, there are many studies regarding Vitamin D deficiency in children with NS, yet study regarding the association between Vitamin D level and blood pressure in children with NS has never been reported.

Methods

This was a cross-sectional, observational analytic study to evaluate the association of serum 25(OH)D level with blood pressure in children with NS. This study was done at Pediatric Outpatient Department and Inpatient Department H. Adam Malik Hospital, Medan, February–August 2019.

Inclusion criteria were children NS with minimal change disease who came to Pediatric Outpatient Department or were admitted to Inpatient Department H. Adam Malik Hospital and not consumption ACE inhibitor (as agent to reduce proteinuria) minimally for 6 weeks. Exclusion criteria were severely malnourished NS, had liver disease, had malabsorption diseases like short bowel syndrome, and those who refused to perform blood examination or not sign-in the informed consent.

Data collection of demographic characteristics, history of illness with diagnosis, and severity of proteinuria were collected from previously diagnosed children with NS. Parents were subsequently explained regarding the study and asked to fill and sign the informed consent. Afterward, physical examination including anthropometric measurements was done. Blood pressure measurement was done when child is seated, with a sphygmomanometer and adjusted blood cuff measurement. Blood pressure examination was done 3 times with 15 min intervals. Mean blood systolic and diastolic pressure values were then measured.

Criteria for blood pressure were done based on the National High Blood Pressure Education Program (NHBPEP) [9]. According to NHBPEP, prehypertension is defined as an average systolic and diastolic blood pressure level that is in 90th percentile to below 95th percentile based on sex, height, and age. In this study, we divided the ages as preadolescent and adolescent, whereas blood pressure elevation in adolescent may be the first clue to underlying renal pathology, or it may be simply a warning sign of future cardiovascular risk.

Venipuncture for 5 ml of venous blood was done for measurements of serum creatinine, albumin, calcium, and 25(OH)D levels. Examination for serum 25(OH)D levels was done by enzyme-linked immunoassay with Mini Vida Brahms®.

Spearman correlation test was analyzed for data which were not normally distributed by SPSS Statistics ver. 20.0. Shapiro–Wilk test was performed to test data distribution. Statistical significance was considered at $P < 0.05$ with a confidence interval of 95%. This study was approved by the Health Research Ethical Committee, Medical Faculty of University of Sumatera Utara/Haji Adam Malik General Hospital, Medan, North Sumatera number 367/TGL/KEPK FK USU-RSUP HAM/2019.

Results

During the study period, there were 35 children with NS included (Table 1), with a median of age 12 years old. The youngest subject enrolled in this study was 2 years old. Sixty percent of the subjects had nephrotic proteinuria. The mean value of serum calcium levels was 7.9 ± 1.0 mg/dl and the mean value of serum 25(OH)D levels was 7.9 (0.7–37.8) ng/ml. Only 20% of the subject had a normal value of serum 25(OH)D levels, while the others had low serum 25(OH)D levels.

Table 1: Subjects characteristics

Characteristics	n=35
Median of age, year (range)	12.0 (2.0–17.0)
Sex, n (%)	
Male	23 (65.7%)
Female	12 (34.3%)
Mean of height, cm (SD)	132.7 (25.5)
Median BMI, kg/m ² (range)	19.0 (12.6–59.3)
Median creatinine levels, mg/dl (range)	0.4 (0.2–2.2)
Mean glomerular filtration rate, ml/min/1.73m ² (SD)	136.9 (52.7)
Median albumin levels, g/dl (range)	2.6 (0.9–5.3)
Proteinuria, n (%)	
Nephrotic	21 (60.0)
Non-nephrotic	14 (40.0)
Mean calcium serum levels, mg/dl (SD)	7.9 (1.0)
Median systolic blood pressure (range)	110.0(90.0–160.0)
Median diastolic blood pressure (range)	70.0 (60.0–100.0)
Median Vitamin D serum levels, ng/ml (range)	7.9 (0.7–37.8)
Category of vitamin D status, n (%)	7 (20.0)
Normal	2 (5.7)
Insufficiency	14 (40.0)
Deficiency	12 (34.3)
Severe deficiency	

The median serum 25(OH)D (Vitamin D) levels were not significantly different among age group categories (Table 2). Association between serum Vitamin D levels with proteinuria category showed there was a significant association, whereas the subjects with nephrotic proteinuria showed lower serum Vitamin D levels compared to subjects with non-nephrotic proteinuria (Table 3).

Table 2: Serum Vitamin D levels based on age group category

Age group category	Median serum Vitamin D levels, ng/ml (range)	p ^a
<5 years old	8.6 (2.0–20.9)	0.784
5–10 years old	8.7 (0.8–37.8)	
>10 years old	7.7 (0.7–27.3)	

^aKruskal–Wallis test.

Figures 1 and 2 showed about correlation between SBP and DBP in preadolescent compared with reference standard for prehypertension based on NHBPEP also for adolescent (Figures 3 and 4).

Table 3: Association of proteinuria with serum Vitamin D levels

	Proteinuria category		p ^a
	Nephrotic	Non-nephrotic	
Median serum Vitamin D levels, ng/ml (range)	4.9 (0.7–15.0)	18.4 (3.6–37.8)	<0.001*
Median systolic blood pressure, mmHg (range)	110.0(90.0–160.0)	100.0(90.0–160.0)	0.039*
Median diastolic blood pressure, mmHg (range)	80.0 (60.0–100.0)	70.0 (60.0–100.0)	0.036*

^aMann–Whitney test, *Significant.

There was also a significant correlation between proteinuria and the systolic and diastolic blood

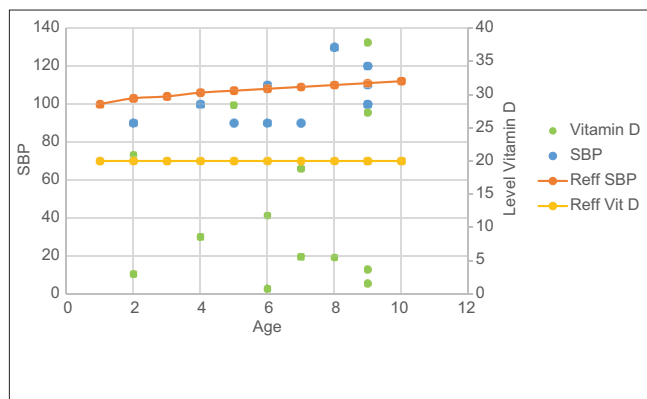


Figure 1: Relationship between systolic blood pressure, level Vitamin D, and age in preadolescent.

pressure, whereas there was an elevation of systolic and diastolic blood pressure in subjects with nephrotic proteinuria compared to their non-nephrotic proteinuria counterparts (Table 4). Correlation of serum Vitamin D levels with systolic and diastolic blood pressure showed a weak negative correlation in preadolescent and adolescent (Figures 1 and 3).

Discussion

This was a hospital-based analytic descriptive, cross-sectional study done from February to August 2019. In this study, we examined the serum Vitamin D levels, proteinuria category, and investigated the association with blood pressure in previously diagnosed children NS with minimal change disease. In this study, the levels of Vitamin D in patients with proteinuria with nephrotic range were lower than those with SN patients with non-nephrotic range proteinuria; this indicates a loss of Vitamin D binding protein through urine in patients with NS.

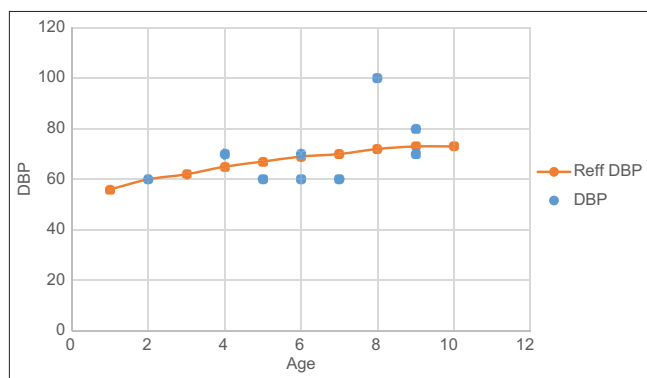


Figure 2: Relationship between diastolic blood pressure and age in preadolescent.

Low levels of Vitamin D are associated with elevated blood pressure. There are a number of plausible physiological mechanisms for this association. Vitamin D deficiency may be linked to the pathophysiology of hypertension through its influence

on the renin-angiotensin system (RAAS). Low level Vitamin D may result in upregulation RAAS. Several studies have shown that low Vitamin D levels affect RAAS activation, through decreased renin gene expression and increased Angiotensin II activity [10], [11].

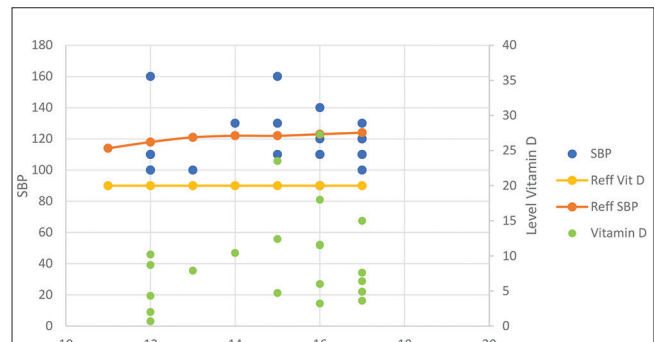


Figure 3: Relationship between systolic blood pressure, level Vitamin D, and age in adolescent.

The positive association between 25 (OH) D levels and flow mediated arterial vasodilatation in chronic kidney disease patients has long been described [12]. Other evidence in animal studies has found that the inactivity of Vitamin D causes decreased expression of endothelial nitric oxide synthase resulting in increased arterial stiffness [13]. Vitamin D also plays an important role to inhibit lipogenesis and stimulate lipolysis; therefore, it has beneficial effect in reducing the risk of calcification in the blood vessels [14].

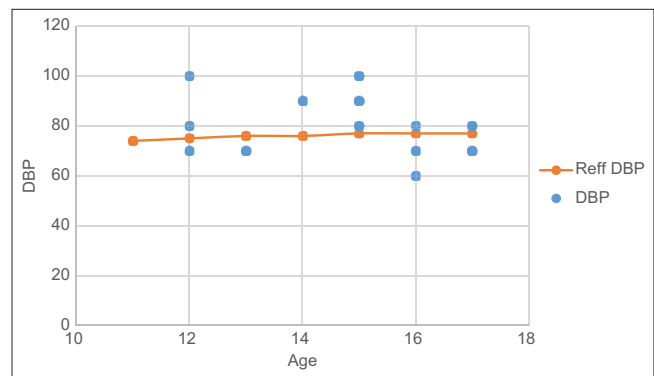


Figure 4: Relationship between diastolic blood pressure and age in adolescent.

In our study, serum Vitamin D levels have been shown to have a weak negative correlation with blood pressure. If we analyze further in Figures 1 and 3, more adolescents have low Vitamin D levels, and their Vitamin D levels are also lower than pre adolescents. Our result is not contradictory with another study by Forman *et al.* that found individuals with deficiency Vitamin D had increased plasma angiotensin II [11]. These data suggest that low Vitamin D levels can lead to upregulation of the renin angiotensin system.

Table 4: Correlation of serum Vitamin D levels and blood pressure

	Median	Range	r	p ^a
Serum Vitamin D levels, ng/ml	7.9	0.7-37.8	-0.114	0.513
Systolic blood pressure, mmHg	110.0	90.0-160.0		
Serum Vitamin D levels, ng/ml	7.9	0.7-37.8	-0.174	0.317
Diastolic blood pressure, mmHg	70.0	60.0-100.0		

^aSpearman correlation test.

Twenty percent of subjects in this study have normal serum Vitamin D levels, while others have a deficiency with severe deficiency category of 34.3% Solanski *et al.* in India showed that 82% of children with NS have serum Vitamin D deficiency and 47% of them are severe deficiency [15]. Similar results were also observed by Illalu *et al.* that showed 20% of subjects with NS have normal serum Vitamin D levels and the others have deficiency and sufficiency of 47% and 32%, respectively [16].

This study shows significant association between serum Vitamin D levels and proteinuria, whereas subjects with nephrotic proteinuria have lower serum Vitamin D levels to those who are non-nephrotic proteinuria. Similar mechanism occurred due to excretion of Vitamin D binding protein through urine. This study is in line with study by Gayk *et al.* that showed lower serum Vitamin D levels on NS patients compared to their non-proteinuric controls [17]. Low serum Vitamin D levels are due to the excretion of Vitamin D-binding proteins in the urine with or without decreased production of 25 (OH) D by the kidneys [18].

Another study from Doorenbos 2012 showed that urinary Vitamin D binding protein is not associated with level plasma Vitamin D except for severe NS. Hence, another possibility that influence level plasma Vitamin D is dietary intake of Vitamin D and sun exposure [19]. In countries with four seasons, adolescent is more aware of the effects of sun exposure than preadolescent so that it can affect vitamin D levels. However, in a tropical country like Indonesia, sun exposure becomes less significant with changes in their Vitamin D levels.

Vitamin D has a role in progression renal damage, as Vitamin D could have antiproteinuric effect. Szeto *et al.* described calcitriol (activated Vitamin D hormone) could decrease proteinuria in ten patients with IgA nephropathy [20]. Similar to minimal change disease, Vitamin D could have effect antiproteinuric combined with angiotensin converting enzyme inhibitor. In our study, we did not consider duration of illness which is about the time since the child was first diagnosed with NS. Hence, the role of Vitamin D as an antiproteinuric, in this study, could not be explained well.

Conclusions

Both Vitamin D deficiency and severe deficiency are observed in children with NS. Serum Vitamin D levels have been shown to have a weak negative correlation with blood pressure in children with NS.

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