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Optimal Vitamin D levels in Children with Chronic Kidney Disease

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Abstract

Background: Vitamin D is an essential component of skeletal development. Although hypovitaminosis D has been widely observed, little data for vitamin D status in pediatric patients with chronic kidney disease (CKD) has been reported. The aim of this study was to assess the prevalence of abnormal vitamin D status and analyze factors associated with inadequate 25(OH) vitamin D (25(OH)D) levels in children with CKD.

Methods: Serum 25(OH)D levels and other parameters associated with vitamin D status were evaluated by a cross-sectional study of pediatric patients with predialysis CKD stage 2-5 at Samsung Medical Center located in Seoul, Republic of Korea. Vitamin D deficiency and insufficiency were defined as a serum 25(OH)D level < 20 ng/mL and 20-30 ng/mL, respectively.

Results: Of the 113 pediatric patients with CKD, vitamin D deficiency or insufficiency was found in 77.8% of the patients and 54.9% had a diagnosis of vitamin D deficiency with a serum 25(OH)D levels below 20 ng/mL. An increasing prevalence of vitamin D deficiency in advanced CKD was observed Age and PTH levels were negatively associated with 25(OH)D levels in pediatric CKD patients.

Conclusion: This study demonstrated that a prevalence of 25(OH)D insufficiency and deficiency are common in children with CKD. The age effect on abnormal vitamin D status was observed in pediatric patients with CKD, and future studies to adjust the guideline for vitamin D supplementation according to the age is needed.

Keywords: Chronic kidney disease; 25(OH) vitamin D deficiency; Children

Introduction

The vitamin D is an essential factor for skeletal development, and its deficiency can cause growth retardation and skeletal deformities such as rickets [1,2]. Vitamin D_3 (cholecalciferol) sourced from diet and ultraviolet B sunlight is metabolized to 25(OH) vitamin D (25(OH)D, calcidiol) in the liver, and then in the kidney to $1,25(OH)_2$ vitamin D ($1,25(OH)_2D$, calcitriol) which is the biologically active form [1,2]. Additionally, non-renal production of $1,25(OH)_2D$ in skin, colon, prostate, macrophage, and parathyroid has been reported [2]. Calcitriol binds to vitamin D receptor (VDR) within the cells, and acts in intestine, bone, immune cells, and tumor microenvironment [2-4]. The VDR has been reported to be found in endocrine glands, cardiovascular tissues, and hematopoietic cells, and vitamin D has been supposed to be involved to both skeletal disease and nonskeletal diseases including metabolic syndrome, insulin resistance, obesity, cardiovascular diseases, infection, allergy, and cancer [2-5].

Among the various forms of vitamin D in body, serum 25(OH) D is used as a parameter to reflect vitamin D status because 25(OH) D can activate VDR and contribute to the overall vitamin D effect on the target organs [2,3]. Although vitamin D deficiency or insufficiency has been emerging as an important health problem in all age groups, no consensus on the definition of vitamin D deficiency in children exists. Usually, the stratifications according to serum 25(OH)D levels (vitamin D deficiency, <20.0 ng/mL; insufficiency, 20.0-29.9 ng/mL; and sufficiency, ≥30.0 ng/mL) has been used.

Vitamin D deficiency or insufficiency is known to be an epidemic of all age populations in many countries, and the main risk factors in pediatric population have been known to include winter season, insufficient outdoor activity, non-white ethnicity, older age, puberty, obesity, female, and low socioeconomic status. Although epidemiologic data on the prevalence of vitamin D deficiency or insufficiency in patients with chronic kidney disease (CKD) are little and sparse, they has been reported to show relatively low levels of 25(OH)D because of low levels of vitamin D-binding protein, little sunlight exposure, malnutrition, dietary restriction, and inadequate ultraviolet B-mediated synthesis of vitamin D in skin [6-8]. In patients with early CKD, dialysis and kidney transplantation, the prevalence of vitamin D insufficiency and deficiency has been reported to be high, and it is also reported that vitamin D deficiency is more common and severe in dialysis patients than in those with early CKD [8].

In CKD patients, bone disorders, hypertension and cardiovascular morbidity seem to be related to vitamin D deficiency [9,10]. It was reported that serum levels of 25(OH)D were also inversely associated with serum level of parathyroid hormone (PTH) in patients with CKD [10]. Therefore, the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for bone mineral metabolism and disease in CKD recommend the measurements of 25(OH)D levels once annually in patients with CKD and supplementation with vitamin D if serum calcidiol level is less than 30 ng/mL [11]. Kidney Disease: Improving Global Outcome (KDIGO) clinical practice guidelines also recommend to check serum 25(OH)D level and correct vitamin D deficiency [12]. However, there is no data how much amount of vitamin D supplementation is necessary for Korean pediatric patients with CKD to maintain the sufficient levels of vitamin D and prevent the vitamin D associated morbidity.

Most studies for the prevalence, risk factors, or the morbidity of vitamin D deficiency in CKD patients were conducted in adults patients, and lack of data about serum 25(OH)D levels in pediatric patients with CKD have been reported. Additionally, there is no consensus for

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replacement with ergocalciferol or cholecalciferol in pediatric patients. In this study, we investigated the prevalence of vitamin D deficiency, other factors which might be associated with vitamin D status, and the optimal vitamin D levels for intervention in pediatric CKD patients.

Methods

This study was approved by Samsung Medical Center Institutional Review Board. A retrospective cross-sectional study was performed in pediatric predialysis CKD patients who followed up at the pediatric nephrology outpatient clinic of Samsung Medical Center between January 1, 2010 and December 31, 2012. Serum 25(OH)D and 1, 25(OH) D levels were assessed at annual blood sampling through all seasons, and other parameters including serum creatinine, alkaline phosphatase, calcium, phosphorus, and intact PTH were collected. Demographic data were also collected.

Patients between ages 1 to 18 years were included if they were diagnosed as CKD and had a measured 25(OH)D level. Patients were excluded from the study if they had been diagnosed with hereditary rickets or parathyroid disease, or history of serious illness or medication affecting bone mineral metabolism. The patients did not use vitamin D supplementation before being enrolled in the study. The sample size was estimated as follows: the significance level of 0.05, the power of 0.8, the predicted difference in mean values and standard deviation for serum 25(OH)D levels. According to the estimations, the number of the patients for each group had to be equal or more than 17.

Serum intact PTH was measured by a chemiluminescence immunoassay. Serum 25(OH)D and $1,25(OH)_2D$ levels were assessed by a radioimmunoassay. Renal function was estimated based on estimated glomerular filtration rate (GFR) using the most recent updated bedside Schwartz calculation [13]. Patients with CKD were stratified into stage 0 to 1 CKD (GFR >90 mL/min/1.73 m^2), stage 2 CKD (GFR, 60 to 90 mL/min/1.73 m^2), stage 3 CKD (GFR, 30 to 60 mL/min/1.73 m^2), stage 4 CKD (GFR, 15 to 30 mL/min/1.73 m^2), or stage 5 CKD (GFR < 15 mL/min/1.73 m^2) based on K/DOQI definitions [11].

Statistical analysis

Comparisons between groups were performed using a chi-square and student t-test for independent samples. In order to analyze the vitamin D status according to CKD stages, the one-way ANOVA technique was used. The relationship between serum 25(OH)D levels and other variables was assessed by Linear regression analysis. For all statistical analyses, $p < 0.05$ was considered to be significant. Statistical analysis was executed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

The characteristics of the studied patients are demonstrated in Table 1. One hundred thirteen patients with CKD were recruited on pediatric nephrology outpatient clinic. All patients were Korean. Their mean serum 25(OH)D levels was 24.1 ng/mL, and the range was from 3.9 to 170.3 ng/mL. Thirty-two patients were previously diagnosed as having solid tumor including neuroblastoma, medulloblastoma, retinoblastoma, and osteosarcoma, and 3 patients as having hematologic malignancy including leukemia and lymphoma. They were disease-free state when 25(OH)D levels were measured.

In pediatric patients with CKD, 88 patients (77.8%) had a serum 25(OH)D levels below 30 ng/mL, and 62 patients (54.9%) had a diagnosis of vitamin D deficiency with a serum 25(OH)D levels below 20 ng/mL. Table 2 revealed the characteristics of the patients according to CKD stage. There was no correlation between 25(OH)D level and CKD stages. However, an increasing prevalence of vitamin D deficiency was found in advanced stage of CKD (CKD stage 2; 37.1%, CKD stage 3; 55.8%, CKD stage 4; 68.8%, CKD stage 5; 73.7%, Figure 1). In patients with CKD, there was no statistical difference in 25(OH) D levels between sunny months and dark months.

Table 3 shows the characteristics of the patients according to serum 25(OH)D level. PTH levels in the group with serum 25(OH)D levels less than 30 ng/mL were higher than patients with sufficient 25(OH) D levels, but there was no significant difference (70.1 ± 76.0 pg/mL vs. 147.3 ± 34.7 pg/mL, P = 0.218). However, PTH levels in the group with serum 25(OH)D levels less than 20 ng/mL were significantly higher than patients with >20 ng/mL (66.4 ± 62.8 pg/mL vs. 177.9 ± 337.4 pg/mL, P = 0.022). Patients with 25(OH) levels less than 30 ng/mL were

Variable	Value
Patients (*n*)	113
Age, years	12.1 (5.6)
Male to female (*n*)	72: 41
Estimated GFR, mL/min/1.73m^2	45.0 (26.0)
Calcium, mg/dL	9.4 (0.7)
Phosphorus, mg/dL	4.4 (1.3)
ALP, U/L	234.9 (306.5)
Intact PTH, pg/mL	128.6 (260.4)
25(OH)D, ng/mL	24.1 (21.9)
1, $25(OH)_2D$, ng/mL	34.2 (18.6)

SD - Standard Deviation; GFR - Glomerular Filtration Rate; ALP - Alkaline Phosphatase; PTH - Parathyroid Hormone; 25(OH)D - 25(OH) vitamin D; 1, $25(OH)_2D$ - 1, $25(OH)_2$ vitamin D;

Table 1: Characteristics (mean, SD) of the enrolled patients.

	CKD Stage2 (*n*=35)	Stage 3 (*n*=43)	Stage 4 (*n*=16)	Stage 5 (*n*=19)
Age, year	12.5 (5.3)	11.7 (5.9)	10.3 (5.2)	13.9 (5.3)
Male: Female (*n*)	21: 14	26: 17	10: 6	15: 4
Estimated GFR, ml/min/1.73m^2	75.2 (9.7)	45.9 (9.8)	22.0 (5.2)	7.2 (3.7)
Serum creatinine, mg/dL	0.8 (0.2)	1.3 (0.4)	2.6 (1.1)	10.5 (5.3)
Serum Calcium, mg/dL	9.4 (0.6)	9.3 (0.8)	9.2 (0.5)	9.7 (0.8)
Serum Phosphorous, mg/dL	41. (0.7)	4.1 (1.0)	4.3 (0.8)	5.9 (2.2)
Serum 25(OH)D, ng/mL	24.5 (13.1)	23.6 (24.1)	22.1 (15.5)	24.2 (33.2)
Serum $1,25(OH)_2D$, ng/mL	31.2 (16.0)	41.1 (21.7)	33.9 (18.6)	26.0 (11.6)
Serum ALP, U/L	182.7 (121.0)	266.1 (360.7)	215.3 (106.5)	183.5 (163.0)
Serum Intact PTH, pg/mL	47.2 (32.2)	134.0 (359.7)	126.4 (104.3)	227.4 (270.3)

SD - Standard Deviation; CKD - Chronic Kidney Disease; GFR - Glomerular Filtration Rate; 25(OH)D - 25(OH) Vitamin D; 1, $25(OH)_2D$ - 1, $25(OH)_2$ Vitamin D; ALP - Alkaline Phosphatase; PTH - Parathyroid Hormone;

Table 2: Characteristics (mean, SD) of patients according to CKD stage.

older than those with sufficient serum 25(OH)D levels (9.2 ± 4.9 years vs. 12.9 ± 5.4 years, P = 0.003).

In the bivariate analysis, the age was negatively correlated with serum 25(OH)D level (P = 0.000) . The levels of PTH were negatively correlated with serum 25(OH)D levels (p = 0.0386, Figure 2). The 25(OH)D cut-off level, predicting a PTH level above 70 pg/mL was 30.27 ng/mL .There was no correlation between serum 25(OH)D level and serum 1,25 $(OH)_2D$, calcium, phosphorus , or alkaline phosphatase.

Discussion

In our study, the vitamin D insufficiency and deficiency are widely prevalent in Korean children with predialysis CKD. The prevalence of serum 25 (OH)D less than 30 ng/mL was 77.8% in pediatric patients with predialysis CKD. Recent data showed that only 2.9% was vitamin D sufficient in Korean children and its prevalence increases in winter-spring season, in overweight children and in older age groups [14]. In Korean children with dialysis in the same unit, vitamin D deficiency and insufficiency were found in 83.0% [15]. Pediatric patients with chronic dialysis in our unit showed mean 25(OH)D levels of below 20 ng/mL, and our predialysis CKD patients above 20 ng/mL. These finding is compatible with the previous results that vitamin D deficiency was more severe in dialysis patients than in early CKD patients.

The recent studies and our findings suggested that vitamin D deficiency is strongly associated with the more advanced stage of CKD [8,10]. Several explanations were possible. First, the pediatric patients with more advanced stage of CKD might be under the condition of more restricted diet and physical activity, and vitamin D deficiency is more common. Second, the patients with advanced CKD and overt proteinuria might have greater loss of urinary vitamin D metabolites which can influence on inadequate vitamin D status such as vitamin D binding protein [16]. The third explanation is that serum 1, 25$(OH)_2D$ functions as a negative endocrine regulator of renin gene expression, and inadequate vitamin D status may affect the development of hypertension and progression of CKD [17].

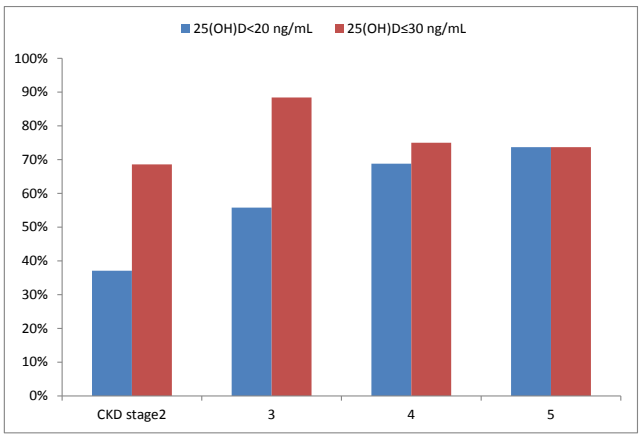

Figure 1: Prevalence of vitamin D insufficiency and deficiency by CKD stage. Data are percentage

In the present study, we found that the age was negatively associated with serum 25(OH)D levels in pediatric predialysis CKD. In Korean children with dialysis and no medical condition, the same findings were observed [14,15]. Chung et al. reported that the proportion of vitamin D deficiency increase with advancing age group from 44.3 % in 4-6 years to 77.0 % in 13-15 years in Korean children [14]. The previous reports performed in pediatric patients with cystic fibrosis suggested that older children were more likely to have vitamin D deficiency comparing with children aged < 5 years [18,19]. Mogayzel et al. reported that 25(OH)D levels decrease by 0.4 ng/mL for each year increase in age in pediatric patient with cystic fibrosis [19]. For these findings, it is supposed that older children have fewer chance of outdoor activity because of competitive entrance examination for university [14]. The daytime activity between 10 AM to 3 PM has been known to be effective for vitamin D synthesis, and outdoor activity is an important factor to prevent vitamin D deficiency in children [14]. The assessment for the time spent for activities is needed to clarify the age effect on vitamin D status.

Compared with patients having vitamin D sufficiency, those with vitamin D insufficiency or deficiency had the tendency to show higher intact PTH levels. González et al. reported that inadequate vitamin D status was associated with secondary hyperparathyroidism in patients with CKD without dialysis [10]. In our study, PTH levels are negatively correlated with 25(OH)D levels, and the significant difference in PTH levels was observed between those with 25(OH)D levels ≥20 ng/mL and with <20 ng/mL. Usually, vitamin D insufficiency is defined as a 25(OH)D levels less than 30 ng/mL, and deficiency as less than 20 ng/mL. KDIGO guidelines recommend to evaluate 25(OH)D levels and correct abnormalities if PTH > upper normal limit of assay in CKD stage 3-5 [12]. There has been no consensus for acceptable PTH levels in each stage of CKD, and upper normal limit of PTH in CKD stage 3-5 was defined as a 70 pg/mL in our study. The cut-off value of 25(OH) D levels predicting a PTH level above 70 pg/mL was 30.27 ng/mL, and these findings suggested that the definition of vitamin D insufficiency less than 30 ng/mL is applicable to initiate the intervention with oral inactive form of vitamin D such as ergocalciferol or cholecalciferol supplementation in Korean children with CKD. K/DOQI clinical practice guideline recommend to prescribe the different dosage and duration of vitamin D supplementation according to serum 25(OH)D levels, and KDIGO clinical practice guideline recommends to correct

	Serum 25(OH)D ≥ 30 ng/mL	Serum 25(OH)D <30 ng/mL	P value
Patients (*n*)	25	88	
Age, years	9.2 (4.9)	12.9 (5.4)	0.003
Male: Female (*n*)	16: 9	56: 32	NS
Serum calcium, mg/dL	9.6 (0.5)	9.3 (0.8)	NS
Serum Phosphorus, mg/dL	4.7 (1.6)	4.4 (1.3)	NS
Serum 25(OH)D, ng/mL	50.3 (34.4)	16.6 (6.4)	0.000
Estimated GFR, mL/min/1.73m^2	48.6 (30.4)	44.1 (24.7)	NS
Serum intact PTH, pg/mL	70.1 (76.0)	147.3 (34.7)	NS
SD - Standard Deviation; CKD - Chronic Kidney Disease; NS - Not Significant; 25(OH)D - 25(OH) Vitamin D; GFR - Glomerular Filtration Rate; PTH - Parathyroid Hormone;			

Table 3: Characteristics (mean, SD) of the patients with CKD by vitamin D status.

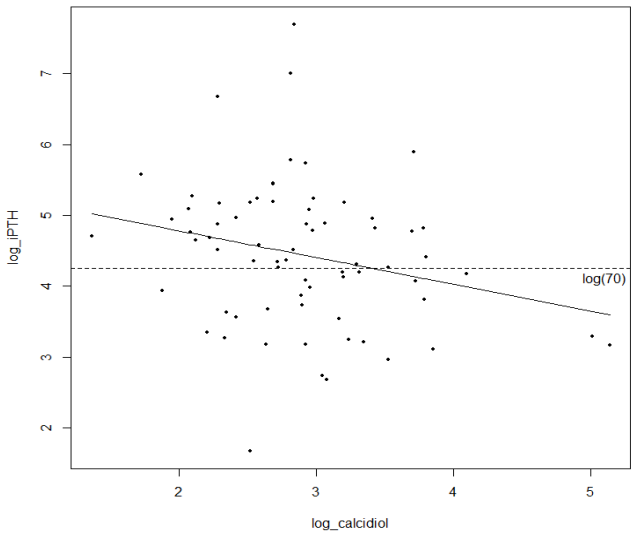

Figure 2: Serum 25(OH)D levels and their association with PTH levels in pediatric patients with chronic kidney disease.

vitamin D deficiency and insufficiency using strategies for the general population [11,12]. Therefore, further studies might be necessary to clarify the optimal dose for vitamin D supplementation to maintain sufficient serum 25(OH)D levels, and long term prognosis associated with vitamin D supplementation in pediatric CKD group. It may be also necessary to reevaluate the current practice and adjust the protocol to increase the dosage of vitamin D supplementation according to not only serum 25(OH)D levels but also the age.

The present study has a few limitations. There was no data about other behavioral or dietary factors such as daily activity, sun exposure, sunscreen use, or milk consumption. Our study included a relatively small number of patients in a single center, and there might be a limitation that our patients might not be representative of all pediatric patients with CKD.

Compared with the dialysis patients, the levels of serum vitamin D are higher, and the prevalence of vitamin D deficiency is lower in predialysis patients. Our data also found that serum 25(OH) vitamin D levels were negatively correlated with the age and PTH levels in pediatric patients with CKD. Therefore, the specific concern for the adolescent patients with advanced CKD is needed to prevent vitamin D deficiency.

Conclusion

This study demonstrated that a prevalence of 25(OH)D insufficiency and deficiency are common in children with CKD. The age effect on abnormal vitamin D status was observed in pediatric patients with CKD, and future studies to adjust the guideline for vitamin D supplementation according to the age is needed.

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