Association of Vitamin D Deficiency with Increased Pulse Wave Velocity and Augmentation Index in Children With Chronic Kidney Disease

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Introduction. It is known that in children with chronic kidney disease (CKD), cardiovascular damage starts in the form of arterial stiffness. There are risk factors other than the traditional ones such as arterial stiffness hypertension, obesity, hypercholesterolemia, and insulin resistance. Vitamin D deficiency is rather common in CKD, and it was introduced as a risk factor for atherosclerosis; however, its relationship with arterial stiffness is not known completely. The purpose of this study was to research the relationship between 25-hydroxyvitamin D levels and arterial stiffness.

Materials and Methods. Arterial stiffness was evaluated by measuring augmentation index (AI) and pulse wave velocity (PWV) from the radial and carotid arteries with a Vicorder. The 25-hydroxyvitamin D levels were measured by an immunoassay method.

Results. In the 81 CKD patients (mean age, 13.21 ± 6.02 years; mean body mass index, 19.42 ± 5.12 kg/m^2; and 56.8% male), the mean vitamin D level was 60.71 ± 39.52 ng/mL, the mean AI was 7.93 ± 7.77%, and the mean PWV was 9.79 ± 4.36 m/s. Serum levels of 25-hydroxyvitamin D was correlated with AI (r = -0.482, *P* = 0.001) and PWV (r = -0.57, *P* = .001).

Conclusions. In this study, it was proven that vitamin D deficiency in children was related to nondiabetic and nondialysis CKD.

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INTRODUCTION

Cardiovascular disease is the most important morbidity and mortality reason in chronic kidney disease (CKD).[1] It was shown that the vascular changes in children with CKD developed in early stages of the disease and were closely related to the advanced stage of cardiovascular disease. One of the most important cardiovascular changes is the stiffening of the large arteries.[2] This condition causes reduced arterial distensibility, high brachial pulse pressure, increased pulse wave velocity (PWV), and augmentation index (AI), and in the end, it leads to left ventricle hypertrophy.[3] Therefore, femoral carotid PWV and AI measurement are measures used for anticipating the cardiovascular case risk and determining the arterial stiffness in CKD.

Underlying pathophysiological processes and courses, which are responsible from vascular changes observed in CKD patients, are unclear. There are multiple pathophysiological factors involved. It was shown that serum calcium, phosphorus, and intact parathyroid hormone (PTH) in pediatric patients with CKD cause arterial wall stiffness.[4] Vitamin D is an important factor playing a significant role in regulating the calcium-phosphorus metabolism. Vitamin D is found in 2 forms in the body: 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol. It has been shown

that vitamin D is associated with cardiovascular system, especially the vascular calcification. Serum 25-hydroxy vitamin D levels are the forms of vitamin D circulating and stored in human body and indicate the vitamin D condition of the body. Vitamin D deficiency may cause atherosclerotic events affecting PWV and AI, which are indicative of endothelial function. In a study conducted in patients with end-stage renal disease, negative effects of vitamin D deficiency on endothelial function were demonstrated.[5] In this study, we aimed to determine the effect of vitamin D deficiency on PWV and AI, which are the indicators of 25-hydroxy vitamin D levels and arterial stiffness in children with CKD.

MATERIALS AND METHODS

A cross-sectional single-centered study was planned, which enrolled 81 predialysis and nondiabetic patients, who were diagnosed to have CKD at the Ege University Medical School Pediatric Nephrology clinics between the dates of March 2016 and March 2018. Approval for the study was taken from the Clinical Research Ethics Committee of Ege University Medical School. Written consent was taken from the parents of the children.

Patients with a diagnosis of diabetes mellitus or with insulin resistance were not included in the study. Patients with the medical history of active systemic vasculitis, active infection, renal vascular abnormalities, cardiovascular abnormalities, and a family history of early cardiovascular diseases were not included in the study. None of the patients received vitamin D treatment; they had no active inflammatory conditions, and they were not taking any immune-suppressing drugs or medicines. Patients' age, sex, CKD etiology, body weight, height, body mass index, and systolic and diastolic blood pressure were measured and recorded. Blood Pressure was measured from the arm with Omron brand automatic device using the oscillometric method. Blood pressure measurements were done by using an arm blood pressure cuff in suitable size after 5 minutes of resting.

The vitamin D concentration was categorized based on the current Kidney Disease Outcomes Quality Initiative guidelines as optimal (> 30 ng/mL), insufficient (15 ng/mL to 30 ng/mL), and deficient (< 15 ng/mL).

Chronic kidney disease was described as a continuation of the kidney dysfunction for more than 3 months. Children between the ages 6 and 17 years with no start of any renal replacement therapy yet and whose estimated glomerular filtration rate (GFR) was between 15 mL/min/1.73 m^2 and 89 mL/min/1.73 m^2 were included in the study. According to GFR, the staging took place as 60 mL/min/1.73 m^2 to 89 ml/min/1.73 m^2 as stage 2; 30 mL/min/1.73 m^2 to 59 mL/min/1.73 m^2 as stage 3; and 15 mL/min/1.73 m^2 to 29 mL/min/1.73 m^2 as stage 4. Estimated GFR was calculated by using the bedside Schwartz formula.[6,7]

Serum levels of urea, creatinine, uric acid, calcium, phosphorus, C-reactive protein, sedimentation, 25-hydroxyvitamin D, intact parathyroid hormone (PTH), cystatin C, glucose, fasting insulin, low- and high-density lipoprotein cholesterol, total cholesterol, and triglyceride were measured quantitatively in blood samples of the patients, which were taken from patients after 12 hours of fasting. Insulin resistance was calculated by the homeostasis model assessment for insulin resistance, the cutoff values of which for insulin resistance were calculated to be 2.67 in boys and 2.22 in girls in the prepubertal period, and 5.22 in boys and 3.82 in girls in the pubertal period.[8,9] The serum 25-hydroxyvitamin D was measured with an Immunodiagnostic Systems kit (UK) using enzyme immunoassay. Serum PTH was measured using ADVIA Centaur XP Immunoassay System (Siemens, England). Serum calcium, phosphorus, creatinine, total cholesterol, triglyceride, and low- and high-density lipoprotein cholesterol were measured with the AU5800 biochemistry analyzer (Beckman Coulter, ABD) automatically. Cystatin C was measured with the Particle Enhanced Nephelometric Immunoassay method. Immunoturbidimetric analyze was measured with reactive (Leadman, China) for urinary protein excretion of 24 hours.

Echocardiography evaluations were performed by the same pediatric cardiologist using two-dimensional M-mode echocardiography with a 3.5-MHz transducer (HP SONOS 1000 System, Philips, Best, The Netherlands). Measurements consisted of interventricular septal thickness, posterior wall thickness, left ventricular (LV) diameter at end-diastole, and LV diameter at end systole. The LV mass was calculated using the formula validated by Devereux and Reichek.[10] The LV mass was

indexed (LVMI) for height 2.7.

Arterial stiffness evaluation, carotid-femoral PWV, and AI measurements were carried out with a Vicorder (Skidmore Medical Limited, Bristol, UK) device. Also the peripheral and central arterial pulse waveforms from radial and carotid arteries were recorded with a Vicorder device. Mean values of the compound radial waveforms were calculated using the computer program prepared solely for this study. The AI was calculated as the difference between central aortic waveforms' first and second systolic peaks, and expressed as the percentage of pulsation length.

Carotid artery ultrasonography was performed to measure carotid intima-media thickness measurement according to a previously described method by an experienced pediatric cardiologist.[11] Measurements were done 3 times and mean values were recorded.

The SPSS software (Statistical Package for the Social Sciences, version 21.0, IBM Corp, New York, NY, USA) was used for analyzes. Numeric variables' suitability to the normal distribution was analyzed with Shapiro-Wilk test. Numeric variables were presented as median (minimum and maximum). Categorical variables were presented as numbers and percentages. The Mann-Whitney U test was applied to compare the mean values of the two independent groups. A *P* value less than .05 was accepted as significance level for all hypotheses.

This study adhered to the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

RESULTS

Eighty-one predialysis children with CKD were included in this study. Demographic and clinical characteristics of the studied population are summarized in Table 1. The children were divided into 2 groups of those with 25-hydroxyvitamin D level less than and higher than 15 ng/mL. A significant difference was determined in the demographic data between the two groups (Table 2). Patients with a 25-hydroxyvitamin D level less than 15 ng/mL had higher values compared to the patients with a 25-hydroxy vitamin D levels higher than 15 ng/mL for LVMI, carotid-femoral PWV, and AI (Table 3).

There were no differences between vitamin D levels of stage 2 to 3 and stage 4 of CKD (*P* = .38). No significant difference was found between vitamin D deficiency and disease stage (*P* = .21; Table 4).

Results of correlation analyses for distinguishing independent determinants of the arterial stiffness in children with CKD are shown in Table 5. Relationships between the variables indicated that 25-hydroxyvitamin D, increased PWV, and arterial stiffness were among the independent determinants. 25-hydroxy vitamin D levels showed negative correlations with arterial stiffness and PWV values (r = -0.57, *P* < .001 and r = -0.48, *P* < .001, respectively).

The PWV and AI values increased as GFR decreased. Estimated GFR was inversely correlated with PWV and AI (r = -0.35; *P* = .001 and r = -0.25,

Table 1. Baseline Demographic Characteristics of the Participants*

Characteristic	Value
Age, y	13.21 ± 6.02
Sex	
Male	46 (56.8)
Female	35 (43.2)
Body mass index, kg/m^2	19.42 ± 5.12
Chronic kidney disease	
Stage 2	24 (29.7)
Stage 3	29 (35.8)
Stage 4	28 (34.5)
25-hydroxyvitamin D, ng/mL	60.71± 39.52
25-hydroxyvitamin D, ng/mL	
< 15	21 (25.9)
15 to 30	28 (34.6)
> 30	32 (39.5)
Augmentation index, %	7.93 ± 7.77
Pulse wave velocity, m/s	9.79 ± 4.36

*Values are mean ± standard deviation or frequency (percentage).

Table 2. Clinical Characteristics of Predialysis Chronic Kidney Diseases Patients With Low and Normal Vitamin D Levels

Characteristic	Vitamin D Deficiency (n = 21)	Normal Vitamin D (n = 60)	*P*
Age, y	14.39 ± 4.35	12.54 ± 5.14	.37
Body mass index, kg/m^2	19.63 ± 4.94	18.56 ± 4.76	.47
Systolic blood pressure, mm Hg	119.40 ± 11.03	109.76 ± 13.89	.16
Diastolic blood pressure, mm Hg	72.40 ± 16.59	71.21 ± 10.41	.23

Table 3. Biochemical Characteristics of Predialysis Chronic Kidney Diseases Patients With Low and Normal Vitamin D Levels

Characteristic	Vitamin D Deficiency (n = 21)	Normal Vitamin D (n = 60)	*P*
Calcium, mg/dL	8.78 ± 1.61	9.12 ± 1.87	.43
Phosphorus, mg/dL	5.32 ± 1.43	5.52 ± 1.62	.47
Calcium-phosphorus product, mg^2/dL^2	45.91 ± 14.23	43.24 ± 11.71	.32
Cystatin C, mg/L	2.32 ± 1.44	2.73 ± 1.25	.95
Glomerular filtration rate, mL/min/1.73 m^2	52.01 ± 22.11	40.63 ± 22.54	.98
24-hour proteinuria, $mg/m^2/h$	37.01 ± 45.14	13.28 ± 20.49	.02
25 hydroxyvitamin D, ng/dL	1.94 ± 3.88	50.31 ± 34.09	< .001
Intact parathyroid hormone, pg/mL	81.8 ± 23.21	72.33 ± 21.71	.16
C-reactive protein, mg/dL	0.34 ± 0.43	0.11 ± 0.73	.45
Erythrocyte sedimentation rate, mm/h	36.61 ± 35.63	34.21 ± 39.42	.71
Total cholesterol, mg/dL	220.20 ± 74.14	210.82 ± 147.31	.09
Triglyceride, mg/dL	112.40 ± 117.07	104.27 ± 113.58	.08
Left ventricular mass index, $g/m^{2.7}$	22.23 ± 7.86	20,01 ± 9.19	.15
Pulse wave velocity, m/s	10.31 ± 4.34	6.42 ± 3.01	.03
Augmentation index, %	15.81 ± 11.11	6.74 ± 6.58	.02
Carotid intima media thickness, mm	0.45 ± 0.06	0.46 ± 0.08	.63

Table 4. Vitamin D Levels by Stage of Chronic Kidney Disease (CKD)

Vitamin D	CKD Stages 2 to 3 (n = 53)	CKD Stage 4 (n = 28)	*P*
25 Hydroxyvitamin D, ng/dL	23.58 ± 4.94	25.58 ± 7.62	.38
25 Hydroxyvitamin D			
< 15 ng/mL	14 (26.4)	7 (25.0)	
≥ 15 ng/mL	39 (73.6)	21 (75.0)	.21

Table 5. Correlations Between Laboratory Results and Arterial Stiffness

Variable	Pulse Wave Velocity		Augmentation Index	
	r	*P*	r	*P*
Calcium	0.14	.21	0.12	.20
Phosphorus	0.04	.91	0.33	.12
Calcium-phosphorus product	0.12	.82	0.23	.32
25 Hydroxyvitamin D	-0.57	< .001	-0.48	< .001
Intact parathyroid hormone	0.12	.23	0.12	.34
Cholesterol	0.19	.82	0.21	.15
Triglycerides	0.12	.91	0.89	.31
Estimated glomerular filtration rate	-0.35	.001	-0.25	.02
Cystatin C	-0.23	.04	-0.22	.06

P = .02, respectively). No correlation was determined between cholesterol and other parameters.

DISCUSSION

Vitamin D endocrine is a hormone that plays a role in inflammatory and endothelial functions. Vitamin D deficiency causes various diseases such as infections, cardiovascular diseases,[12] endothelial dysfunction,[13] certain neoplasm types, insulin resistance, and autoimmune diseases.[14] In vitamin D deficiency, inflammation increases through the activation of the renin-angiotensin-aldosterone system, and it is thought that this condition causes endothelial dysfunction.[15]

It has been reported that measured indicators (AI and PWV) of arterial stiffness in children with CKD has increased.[4] The fact that makes this study different than the others is that the effect of Vitamin D deficiency on arterial stiffness is shown independently from factors such as systolic and diastolic blood pressure, obesity, and insulin resistance.[16]

We found out that the serum 25-hydroxyvitamin D concentration is low in 25.6% of children with

CKD. In a study conducted in China, this percentage was reported as 97% for children with CKD.[17] Vitamin D deficiency, in a study conducted in Colombia, was found as 8.8%.[18] There are numerous reasons for the differences in the reports. Serum vitamin D levels are affected by numerous factors such as poor nourishment, race, solar exposure, and geographical region. Our purpose in this study was not determining the prevalence of vitamin D deficiency. Therefore, there were no variables related to vitamin D deficiency that were evaluated or taken into consideration.

We found a significant negative correlation between the 25-hydroxyvitamin D levels and creatinine, phosphorus, calcium-phosphorus product, 24-hour urine protein excretion, and intact PTH levels.[18] In another similarly conducted study, Feng and colleagues found an inverse correlation with serum 25-hydroxyvitamin D levels and GFR, serum phosphorus, PTH, serum creatinine, serum cystatin C, and serum total cholesterol levels, and 24-hour urinary protein discharge.[17] In our study, no significant relationship was found between 25-hydroxyvitamin D levels and calcium, phosphorus, and parathyroid hormone levels. This is different from certain studies performed earlier and it may be due to the relatively low sample size in our study. Urinary proteinuria was significantly higher in cases with vitamin D deficiency in our study, which was similar to other studies found in the literature.[19]

Estimated GFR showed a negative correlation with arterial stiffness; in this case, it was supported that the increased arterial stiffness has a relationship with kidney function disorder.

It makes us think that the majority of the cardiovascular complications in CKD are related to the progress of CKD and D hypovitaminosis.[20] In a study conducted on 34 children with 18 of them suffering from CKD, Patange and colleagues showed that vitamin D levels were inversely correlated with LVMI ($r = 0.54$; $P < .05$). There was no significant difference in the mean LVMI according to the ones having normal (regular) D vitamin in CKD with vitamin D deficiency in our study.[21]

It is considered that vitamin D deficiency in patients suffering from CKD causes cardiovascular damage by causing insulin resistance, hypertension, and hypercholesterolemia. In our study, there was no significant difference in terms of hypertension, body mass index, and hypercholesterolemia between the two groups with and without vitamin D deficiency, and the patients with insulin resistance were not included in the study. No difference was found between traditional risk factors between the cases with and without vitamin D deficiency. Correlation with vitamin D deficiency as independent of other cardiovascular risk factors of increased arterial stiffness was shown.

It was shown that independently from other risk factors, vitamin D deficiency affects arterial stiffness in CKD patients. Vitamin D may act by a different mechanism that forms atherosclerosis. Vitamin D may have the potential of regulating the atherosclerotic course through complex ways. This may shed light on new therapies that can control the atherosclerotic course by aiming to certain proteins in those ways. On these cardiovascular changes observed, Vitamin D is a parameter that is required to conduct studies over in the future.

CONCLUSIONS

In this study, arterial stiffness, which is the very important first stage of atherosclerosis in pediatric patients with CKD, was investigated. This is the very first evidence that relates vitamin D deficiency in children suffering from chronic kidney disease with arterial stiffness. It is necessary to have future studies to explore the mechanism of these changes and see if vitamin D treatment helps in recovery from arterial stiffness.

CONFLICT OF INTEREST

None declared.

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