25-Hydroxyvitamin D Levels and Vascular Calcification in Predialysis and Dialysis Patients with Chronic Kidney Disease

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Key Words

Chronic kidney disease • 25-Hydroxyvitamin D • Pulse wave velocity • Vascular calcification

Abstract

Background/Aims: The role of vitamin D in the process of vascular calcification is unclear in patients with chronic kidney disease. We investigated whether serum 25-hydroxyvitamin D [25(OH)D] is associated with vascular calcification in predialysis and dialysis patients. **Methods:** We included 86 predialysis and 139 dialysis patients. The simple vascular calcification score (SVCS) was evaluated by examining plain X-rays of the pelvis and hands as described previously. The carotid-to-femoral pulse wave velocity (CF-PWV) was assessed with a commercially available device. **Results:** We found a high prevalence of vitamin D deficiency in our population (78.2%). Vascular calcification was present in 46.2% of all patients. Higher calcification (SVCS >3) was significantly associated with lower 25(OH)D levels in predialysis and dialysis patients. Multiple logistic regression analysis for SVCS >3 showed that 25(OH)D levels were negative independent predictors in predialysis (OR: 0.781; 95% CI: 0.623–0.908, $p = 0.019$) and dialysis patients (OR: 0.805; 95% CI: 0.749–0.853, $p = 0.009$). Lower 25(OH)D levels were associated with higher CF-PWV in predialysis patients, but this inverse relation-

ship was no longer present in multivariate analysis. **Conclusion:** We showed an independent relationship between low serum 25(OH)D levels and vascular calcification in both predialysis and dialysis patients.

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Introduction

Patients with chronic kidney disease (CKD), regardless of whether they undergo dialysis or not, are consistently reported to have a high prevalence of vitamin D deficiency [1, 2]. 25-Hydroxyvitamin D [25(OH)D] deficiency is considered a risk factor for hypertension, chronic heart failure, hyperparathyroidism, various cancers, and autoimmune diseases [1]. Indeed, in both the general population and patients with CKD, recent studies have repeatedly reported an association between higher mortality and low 25(OH)D levels [1, 3].

Vascular calcification is a common manifestation of CKD [4, 5]. This disorder is associated with aortic stiffness and is predictive of subsequent cardiovascular dis-

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ease (CVD) and increased mortality [5]. The role of vitamin D in the process of vascular calcification is unknown. Experimental studies have shown that excessive vitamin D induces vascular calcification [6]. However, the relevance of these experimental studies in humans is not clear, as vitamin D toxicity is relatively rare in practice. Contrary to the relationship between excessive vitamin D and vascular calcification, in experimental uremic models, low levels of vitamin D have been associated with extensive vascular calcification, a phenomenon very similar to the vascular pathology seen in patients with CKD [7].

The aim of this cross-sectional study was to investigate the prevalence of vascular calcification in predialysis and chronic hemodialysis patients, and to analyze the association between serum 25(OH)D levels and vascular calcification.

Patients and Methods

Patients

After obtaining approval from the Institutional Review Board of the Bundang CHA General Hospital, 225 patients were recruited. Criteria for inclusion were age 20–90 years and a confirmed diagnosis of CKD [defined as being on dialysis or having two previously estimated glomerular filtration rate (eGFR) values <60 ml/min/1.73 m² calculated according to the equation of the Modification of Diet in Renal Disease Study Group and obtained at an interval of 3–6 months]. Patients were categorized according to CKD stage and K/DOQI guidelines [8, 9]. Patients categorized as CKD stage 5D were on hemodialysis three times per week (≥12 h/week) for at least 3 months without exposure to renal transplantation. Patients with acute infectious diseases, unstable vital signs, or neoplastic illness were excluded. None of the participants were on active vitamin D, vitamin D analogues, warfarin, steroids, or anticonvulsants during the month before study entry. All patients provided written informed consent and participated during the winter period.

Measurements

Blood pressure was measured after 15 min of recumbency. Pulse pressure (PP) was calculated using the formula: PP = SBP – DBP, where SBP and DBP are systolic and diastolic blood pressure, respectively. Arterial stiffness was assessed using a commercially available device (VP-2000; Colin, Komaki, Japan) for pulse wave velocity (PWV) measurements. Pulse wave forms were obtained from the carotid and femoral artery after 15 min of recumbency [9]. Measurements were obtained before the last hemodialysis of the week in chronic hemodialysis patients. All measurements were performed by a single investigator who was blinded to the clinical data, including the participant's CKD status.

Vascular Calcification Score

Vascular calcifications were evaluated with plain X-rays of the pelvis and hands [10]. A simple vascular calcification score (SVCS) was calculated by a single investigator blinded to the clinical data.

X-rays of the pelvis were divided into four sections, and each hand film was divided into two sections. The presence of linear calcifications in each section was scored as 1, and the absence of calcifications was scored as 0. The total score was the sum of all sections and ranged from 0 to 8.

Blood Chemistry

All blood chemistry measurements were determined with samples that were drawn before the hemodynamic study and included serum albumin, serum high-sensitive C-reactive protein (CRP), blood lipids, serum phosphates, and calcium. Serum calcium was adjusted for serum albumin [11]. The total intact parathyroid (iPTH) hormone level was evaluated with an electrochemiluminescence immunoassay. Serum levels of 25-hydroxy-vitamin D₂ + D₃ were measured using a chemiluminescent immunoassay (LIAISON®; DiaSorin, Saluggia, Italy). Levels of 1,25(OH)₂D₃ were determined using a ¹²⁵I radioimmunoassay (DiaSorin). Based on previously published studies, vitamin D deficiency was considered at serum 25(OH)D levels <15 ng/ml, vitamin D insufficiency at levels of 15–30 ng/ml, and serum levels >30 ng/ml were regarded as adequate levels of vitamin D [12].

Statistical Analysis

Results of continuous variables were expressed as means ± SD and of categorical variables as frequencies. For univariate analysis, the unpaired Student t test, ANOVA, or the χ^2 test was used, depending on the characteristics of the variables. Pearson's correlation coefficients were used to assess the relationship among biochemical, clinical, and 25(OH)D levels. As reported in previous studies, SVCSs >3 are associated with an increase in the rate of CVD [10]. Accordingly, multivariate analysis consisted of a stepwise binary logistic regression between SVCSs >3 or ≤3 and the following variables: sex, diabetes, eGFR, phosphorus, iPTH, hemoglobin, CRP, 1,25(OH)₂D₃, carotid-to-femoral PWV (CF-PWV), and 25(OH)D levels in predialysis patients, and diabetes, previous CVD history, calcium, CRP, 1,25(OH)₂D₃, CF-PWV, Ca-containing P binder, and 25(OH)D levels in hemodialysis patients. A value of $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS for Windows (version 17; SPSS, Chicago, Ill., USA).

Results

Baseline clinical and biochemical characteristics are shown in table 1. Of the patients studied, 38.2% were predialysis patients and their eGFR was 33.6 ± 15.7 ml/min/1.73 m². Of these patients, 44.3% were stage 3, 39.3% were stage 4, and 16.4% were stage 5. Chronic hemodialysis patients comprised 61.8% of the patients studied, and their mean duration of dialysis was 44.7 ± 49.6 months. The mean Kt/V of chronic hemodialysis patients was 1.4 ± 0.4 .

The mean 25(OH)D serum level was 13.9 ± 7.2 ng/ml in predialysis patients and 10.6 ± 6.3 ng/ml in dialysis patients. Analysis using the Pearson's correlation coefficient

cient revealed an inverse correlation between serum 25(OH)D levels and eGFR (Pearson = 0.392, $p < 0.001$) in predialysis patients. The prevalence of 25(OH)D deficiency increased with increasing CKD stage in predialysis patients (ranging from 63 to 64, and 73.4% for CKD stages 3, 4 and 5). Most of the patients had vitamin D deficiency (65.1 and 86.3% of predialysis and dialysis patients, respectively), and only a few patients had an adequate level (2.3 and 2.2% of predialysis and dialysis patients, respectively; table 1).

SVCS yielded 38 (44.2%) in predialysis patients and 66 (47.5%) in dialysis patients with calcification. Amongst them, 20 (23.3%) and 42 (30.2%) had an SVCS >3 , respectively. Table 2 shows the differences in epidemiologic, clinical, and laboratory results between patients with SVCS >3 and ≤ 3 . Predialysis patients with higher calcification scores had diabetes, higher PP, higher CF-PWV, higher level of blood urea nitrogen, higher phosphate and iPTH, and lower eGFR, hemoglobin, and 25(OH)D. Among dialysis patients, the variables associated with an SVCS >3 were prevalence of diabetes, history of CVD, higher PP, higher CF-PWV, and serum calcium, and a lower 25(OH)D level.

In multivariate analysis, eGFR ($p < 0.001$), CF-PWV ($p = 0.002$), and 25(OH)D levels ($p = 0.019$) were determined to be independent predictors of an SVCS >3 in predialysis patients. Among dialysis patients, independent predictors of an SVCS >3 were diabetes ($p < 0.003$), CF-PWV ($p = 0.040$), and 25(OH)D levels ($p = 0.009$). Levels of 25(OH)D were negative predictors of higher calcification scores in both predialysis and dialysis patients (table 3). Using univariate logistic regression, lower 25(OH)D levels were associated with the highest CF-PWV tertile [odds ratio (OR): 0.085; 95% confidence interval (CI): 0.08–0.09; $p = 0.008$] in predialysis patients, but this inverse association was abolished after adjusting for age and gender (data not shown).

Discussion

The results of this study revealed a high prevalence of 25(OH)D deficiency and insufficiency in predialysis and chronic dialysis patients. Most importantly, there was a significant relationship between vascular calcification and low serum 25(OH)D levels even in multivariate analysis in both patients.

The mechanisms regulating vascular calcification are under investigation. Extensive studies have shown that vascular calcification is an active, cell-regulating process

Table 1. Baseline characteristics of the study cohort

	Predialysis	Dialysis
Patients, n (%)	86 (38.2)	139 (61.8)
Age, years	61.9 $\pm$ 12.6	57.5 $\pm$ 12.9
Males, %	76.7	56.8
Diabetes, %	55.8	50.4
BMI	25.0 $\pm$ 3.1	22.2 $\pm$ 3.1
Previous CVD, %	27.9	38.8
Coronary, %	4.7	18.7
Cerebrovascular, %	23.3	28.8
Peripheral VD, %	4.7	14.5
eGFR, ml/min/1.73 m ²	33.6 $\pm$ 15.7	6.2 $\pm$ 6.3
SBP, mm Hg	137.4 $\pm$ 20.5	144.1 $\pm$ 25.5
PP, mm Hg	56.7 $\pm$ 14.0	62.3 $\pm$ 16.3
CF-PWV, m/s	1.7 $\pm$ 5.0	1.6 $\pm$ 4.8
WBC, 10 ³ /μl	6.6 $\pm$ 1.9	6.3 $\pm$ 1.9
Hemoglobin, g/dl	11.8 $\pm$ 1.7	10.5 $\pm$ 2.7
Albumin, mg/dl	4.3 $\pm$ 0.4	4.0 $\pm$ 0.4
BUN, mg/dl	35.6 $\pm$ 17.8	63.9 $\pm$ 20.8
Calcium, mg/dl	9.1 $\pm$ 0.6	9.2 $\pm$ 1.0
Phosphate, mg/dl	3.7 $\pm$ 1.0	4.8 $\pm$ 1.7
iPTH, pg/dl	63.9 $\pm$ 55.2	189.7 $\pm$ 281.8
CRP, mg/dl	0.2 $\pm$ 0.4	0.6 $\pm$ 1.7
1,25(OH) ₂ D, ng/ml	32.0 $\pm$ 15.4	22.5 $\pm$ 8.2
25(OH)D, ng/ml	13.9 $\pm$ 7.2	10.6 $\pm$ 6.3
Normal (>30 ng/ml), %	2.3	2.2
Insufficiency (15–30 ng/ml), %	32.6	11.5
Deficiency (<15 ng/ml), %	65.1	86.3
SVCS, 0–8	1.5 $\pm$ 2.0	2.3 $\pm$ 3.0
SVCS ≥ 3 , %	23.3	30.2
Medication		
ACEI/ARB, %	86.0	73.0
Statin, %	48.8	46.7
Ca-containing P binder, %	11.6	70.8

Results are expressed as means $\pm$ SD or numbers (%). ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; VD = vascular disease; WBC = white blood cell count.

similar to bone formation involving many complex cell-related and chemical events, e.g. the active participation of a number of calcification inducers/promoters and inhibitors [5]. Recently, retrospective observational studies suggested that vitamin D provides a survival advantage for patients with CKD [13]. However, evidence for the role of vitamin D in vascular calcification is still inconsistent [6, 7].

In 1997, Goldsmith et al. [14] proposed that higher 1,25(OH)₂D₃ levels are associated with increased vascular calcification in long-term hemodialysis patients in a retrospective study, whereas Shroff et al. [15] reported a bimod-

Table 2. Relationship between SVCS and clinical laboratory variables

	Predialysis patients			Dialysis patients		
	SVCS ≤ 3 (n = 66)	SVCS > 3 (n = 20)	p value	SVCS ≤ 3 (n = 97)	SVCS > 3 (n = 42)	p value
Age, years	60.6 $\pm$ 12.3	66.1 $\pm$ 13.1	0.086	56.3 $\pm$ 13.8	60.1 $\pm$ 10.1	0.072
Males, %	81.8	60.0	0.044	60.8	47.6	0.150
Diabetes, %	42.4	100.0	<0.001	33.0	90.5	<0.001
BMI	25.2 $\pm$ 3.0	24.6 $\pm$ 3.5	0.495	22.4 $\pm$ 3.1	21.6 $\pm$ 3.1	0.195
Previous CVD, %	30.3	20.0	0.371	30.9	57.1	0.004
Coronary, %	5.9	0.1	0.262	14.4	28.6	0.050
Cerebrovascular, %	24.2	20.2	0.696	20.6	47.6	0.001
Peripheral VD, %	6.0	0.1	0.262	8.3	28.6	0.002
eGFR, ml/min/1.73 m ²	37.5 $\pm$ 15.0	20.4 $\pm$ 9.7	<0.001	6.7 $\pm$ 7.5	5.3 $\pm$ 1.4	0.077
SBP, mm Hg	132.6 $\pm$ 18.2	152.9 $\pm$ 20.4	<0.001	143.6 $\pm$ 25.0	145.5 $\pm$ 27.1	0.685
PP, mm Hg	53.2 $\pm$ 12.6	68.3 $\pm$ 11.9	<0.001	60.2 $\pm$ 16.0	67.0 $\pm$ 16.8	0.023
CF-PWV, m/s	15.1 $\pm$ 4.0	21.9 $\pm$ 4.9	<0.001	15.0 $\pm$ 4.0	19.0 $\pm$ 5.4	<0.001
WBC, 10 ³ / μ l	6.4 $\pm$ 1.7	7.2 $\pm$ 2.5	0.155	6.2 $\pm$ 1.9	6.5 $\pm$ 1.8	0.350
Hemoglobin, g/dl	12.2 $\pm$ 1.5	10.5 $\pm$ 1.4	<0.001	10.6 $\pm$ 3.2	10.1 $\pm$ 0.7	0.286
Albumin, mg/dl	4.4 $\pm$ 0.4	4.1 $\pm$ 0.5	0.152	4.0 $\pm$ 0.4	4.0 $\pm$ 0.5	0.855
BUN, mg/dl	30.7 $\pm$ 15.7	52.0 $\pm$ 14.0	<0.001	64.6 $\pm$ 22.3	62.4 $\pm$ 17.0	0.575
Calcium, mg/dl	9.2 $\pm$ 0.5	9.0 $\pm$ 0.7	0.197	9.1 $\pm$ 0.9	9.5 $\pm$ 1.0	0.035
Phosphate, mg/dl	3.5 $\pm$ 0.9	4.5 $\pm$ 0.8	<0.001	4.9 $\pm$ 1.9	4.7 $\pm$ 1.2	0.732
iPTH, pg/dl	55.0 $\pm$ 43.8	93.2 $\pm$ 76.8	0.045	196.7 $\pm$ 259.3	173.5 $\pm$ 330.4	0.657
CRP, mg/dl	0.2 $\pm$ 0.4	0.2 $\pm$ 0.3	0.437	0.5 $\pm$ 1.7	0.7 $\pm$ 1.4	0.540
1,25(OH) ₂ D, ng/ml	34.6 $\pm$ 16.4	23.6 $\pm$ 6.7	0.005	23.2 $\pm$ 8.0	20.8 $\pm$ 8.4	0.106
25(OH)D, ng/ml	15.7 $\pm$ 7.1	7.8 $\pm$ 3.3	<0.001	12.1 $\pm$ 6.8	7.0 $\pm$ 2.7	<0.001
Medication						
ACEI/ARB, %	84.4	100	0.061	69.8	80.5	0.198
Statin, %	48.5	50.0	0.906	45.8	48.8	0.752
Ca-containing P binder, %	9.1	20.0	0.185	78.1	53.7	0.004

Results are expressed as means $\pm$ SD or numbers (%). ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; VD = vascular disease; WBC = white blood cell count.

al association of vitamin D levels and vascular calcifications in children on dialysis. However, compared with the 25(OH)D concentration, circulating 1,25(OH)₂D₃ is a less robust biomarker and has a shorter half-life [16]. The level of 1,25(OH)₂D₃ is tightly regulated by renal 1 α -hydroxylase activity; thus, associations with circulating 1,25(OH)₂D₃ levels may be confounded by factors that affect the activity of this enzyme, including kidney function, diabetes, serum phosphorus, parathyroid hormone, and acid base status [16]. Accordingly, vitamin D deficiency is defined as low serum 25(OH)D levels [12]. Meanwhile, Barreto et al. [17] suggested that vascular calcifications are independent of serum 25(OH)D levels in CKD patients, including dialysis patients. However, Garcia-Canton et al. [12] reported inverse associations between 25(OH)D and vascular calcifications in CKD 4–5 patients. High variability in 25(OH)D measurements might affect these dis-

crepancies. Serum 25(OH)D levels are affected by seasonal variation and by the assessment method. Serum levels of 25-hydroxyvitamin D₂ + D₃ were checked with a chemiluminescent immunoassay (LIAISON, DiaSorin), which is presently the most recommended method. Moreover, in our study, 25(OH)D levels were measured during the winter period in all participants. Further, patients who were treated with anticonvulsants or steroids which affect serum vitamin D levels were excluded.

Another strength of our study is the homogeneity of the participants in each group made possible by the nature of a single-center study. Also, we excluded all participants on all forms of vitamin D supplement (including active vitamin D or vitamin D analogues) during the month prior to the study start and only included hemodialysis patients who had been receiving hemodialysis for > 3 months, thrice a week (≥ 12 h/week), and were

Table 3. Binary logistic regression analysis with SVCS >3 or ≤3

	OR (95% CI)	p value
Predialysis patients		
eGFR	0.901 (0.853–0.955)	<0.001
CF-PWV	1.003 (1.001–1.005)	0.002
25(OH)D	0.781 (0.623–0.908)	0.019
Dialysis patients		
Diabetes, absent/present	6.689 (1.856–24.101)	0.003
CF-PWV	1.002 (1.001–1.003)	0.040
25(OH)D	0.805 (0.749–0.853)	0.009

without exposure to renal transplantation. Most tissues and cells in the body have a vitamin D receptor and this vitamin has multiple functions [13]. On the one hand, vitamin D may favor vascular calcification, e.g. via the regulation of mineral metabolism. On the other hand, vitamin D may protect vessels from vascular calcification, e.g. via the regulation of the cell cycle and modulation of the inflammatory responses. Although some studies report that high calcium, phosphate, and iPTH levels promote calcification [18, 19], we did not find a persistent relationship between phosphate, calcium, and iPTH levels and vascular calcification in multivariate analysis. In our population, serum phosphate, calcium, and iPTH levels were within the normal range according to the KDIGO guidelines. In addition, our data showed that only the association between lower 25(OH)D concentrations and vascular calcification was independent of previously established risk factors for vascular calcification. Therefore, the protective role of vitamin D regarding vascular calcification may become prominent when phosphate, calcium, and iPTH are well controlled.

In this study, analysis of clinical and epidemiological variables revealed associations between vascular calcification and diabetes and arterial stiffness parameters (PP and CF-PWV). Patients with vascular calcification tended to be older, but the data were not significantly different, possibly due to the small study cohort. These findings are in agreement with previously published studies, in which calcifications are generally related to age, diabetes, race, arterial hypertension, and dialysis duration [20]. It should be noted that our patients were relatively younger and included stage 3 CKD as well as fewer diabetic patients compared to those in previous reports [12]. Furthermore, the mean duration of hemodialysis in our patients was 44.74 ± 49.6 months, which

is shorter than the mean dialysis duration reported in a previous study [10]. Those differences may contribute, at least in part, to the lower prevalence of vascular calcification observed.

A very high prevalence of hypovitaminosis D (<30 ng/ml) was observed in both predialysis and dialysis patients. In both groups combined, 19.6% had insufficient levels and 78.2% were considered deficient. Of note, our study was conducted during the winter. Burnand et al. [21] reported low levels of 25(OH)D in the winter in the Swiss population, and Tolouian et al. [22] have observed marked seasonal variations in the vitamin D status in hemodialysis patients. Surprisingly, the prevalence of hypovitaminosis D was as high in predialysis patients as in chronic hemodialysis patients in our study. Food intake habits including low dairy product consumption and the skin color of the Asian population may aggravate hypovitaminosis D.

It is also noteworthy that even in the situation of vitamin D deficiency, lower 25(OH)D levels might have affected vascular calcification. According to our data, the mean level of 25(OH)D was 7.8 ± 3.3 ng/ml in predialysis patients with SVCSs >3, and 7.0 ± 2.7 ng/ml in dialysis patients with SVCSs >3 (table 2). Higher SVCSs (>3) have been found to be correlated with mortality in CKD patients [10]. A level of 5–15 ng/ml 25(OH)D is classified as mild vitamin D deficiency and < 5 ng/ml of 25(OH)D is classified as severe vitamin D deficiency in K/DOQI practice guidelines [8]. A more specific cutoff value for 25(OH)D that is associated with clinical prognosis in CKD patients is required to be able to offer a more appropriate therapy to these patients.

The association between CF-PWV and 25(OH)D levels was significant only in univariate analysis. CF-PWV is a noninvasive and reliable indicator of arterial stiffness, but there are many confounders that affect CF-PWV, such as correction of uremia [23], hypertension [24], the use of renin-angiotensin-aldosterone system antagonists [25], and/or statins [26]. Further studies in a larger study cohort are required to confirm our findings.

This study has several limitations. Being a cross-sectional study, the associations described herein should be interpreted with caution and do not imply a pathophysiological relationship of causality. The small number of patients included in this study may have affected the power of the study. Dietary calcium intake was not quantified and outdoor activities were not investigated. We have only analyzed the percent use of Ca-containing phosphate binders in each group without determining the exact amount or drug type.

In conclusion, the present study indicates a high prevalence of vitamin D deficiency in predialysis and dialysis patients, especially during the winter. Also, we showed an association between low 25(OH)D levels and vascular

calcification in the same population. We propose that vitamin D supplementation may be beneficial for vascular health if the serum level of phosphate, calcium, and iPTH are well controlled.

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