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Study on the relationship between serum 25-hydroxyvitamin D levels and vascular calcification in hemodialysis patients with consideration of seasonal variation in vitamin D levels

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ABSTRACT

Background/aims: The aim of this study was to determine the prevalence of vitamin D deficiency in hemodialysis (HD) patients and the relationship between seasonal variations in vitamin D levels and vascular calcification.
Methods: As a prospective observational study, we analyzed 289 HD patients. We have assessed serum 25-hydroxyvitamin D (25D) levels at the end of the summer (September) and winter (March) and analyzed the data to reveal the association of serum 25D level with vascular calcification scores (VCS) at the end of the summer, when vitamin D levels were found to peak. Plan X-ray images of lateral lumbar spine from all subjects were studied for calculation of semiquantitative VCS as described by Kauppila.
Results: The prevalence of 25D deficiency was 86.2% at the end of the summer and increased to 96.2% at the end of the winter. Female gender and diabetes were associated with vitamin D deficiency. According to univariate analysis, 25D levels were inversely related to vascular calcification. However, after correcting for confounding factors, this relationship lost statistical significance. Multivariate analysis showed that age, systolic blood pressure, and LDL-cholesterol levels were directly associated with a higher VCS.
Conclusion: Vitamin D deficiency was highly prevalent in HD patients with marked seasonal variation. However, low 25D levels could not be identified as an independent predictor of vascular calcification in these patients.

1. Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality among patients with end-stage renal disease (ESRD) [1]. Although there are many traditional risk factors that contribute to the development of this disease, CVD is also associated with non-traditional risk factors in ESRD patients such as mineral bone disease and oxidative and inflammatory states [2]. Vascular calcification is also very common and has recently been considered an important predictor of mortality in ESRD patients [3]. Consequently, vascular calcification scores (VCSs) have been evaluated in hemodialysis (HD) patients using various methods [4–7].

Vitamin D, a pleotropic steroid hormone involved in bone and mineral metabolism and extra-skeletal activity, is associated with lower mortality rates [8]. The potential ameliorating effects of vitamin D on CVD include mechanisms related to the development of vascular calcification and atherosclerosis [9]. Accelerated atherosclerosis may partially explain the associations of vitamin D deficiency with CVD and death. Low 25-hydroxyvitamin D (25D) concentrations are associated with a number of established factors for atherosclerosis [10,11]. Moreover, vitamin D seems to regulate additional inflammatory and immunologic pathways implicated in the development of atherosclerosis [12,13]. The presence of 1-α hydroxylase, which converts 25D to calcitriol, in vascular smooth muscle cells suggests that vitamin D may also have direct effects on the vascular wall, potentially preventing vascular calcification [14,15]. An assessment of the relationship between 25D and vascular calcification could lead to important insights for predicting CVD risk. However, despite evidence linking low vitamin D levels to CVD risk, there remains wide debate about the role of serum vitamin D metabolites, including 25D, in CVD risk because some studies have also reported associations between increased levels of vitamin D metabolites and CVD risk [16]. The effects of vitamin D on vascular calcification appear to follow a biphasic pattern, with both excess and deficiency promoting its development [17]. Conversely, some studies have shown that there is no association between 25D levels and aortic calcification [18–20]. Furthermore, seasonal variations in vitamin D status have

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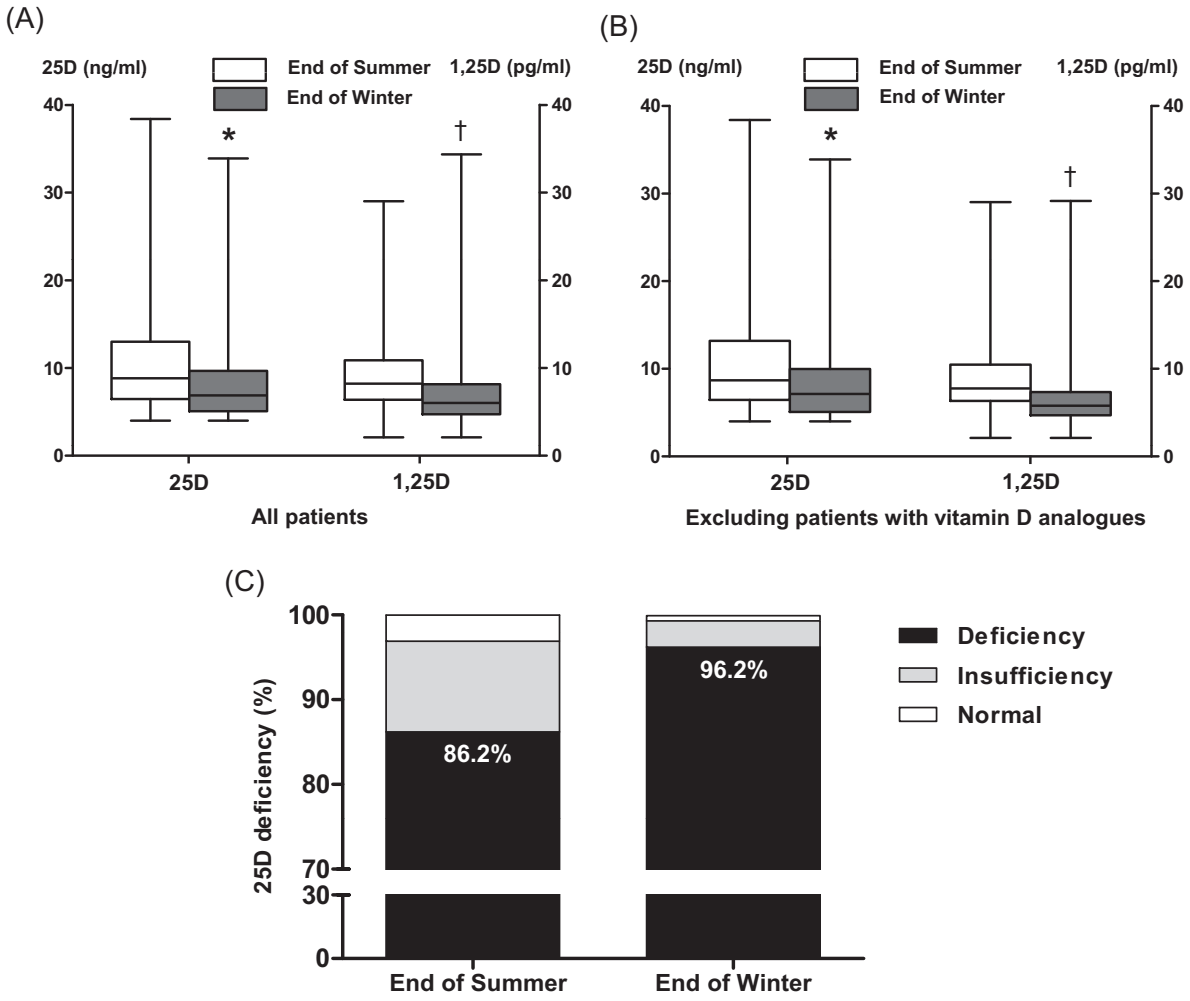

Fig. 1. Seasonal change in serum vitamin D levels in HD patients. *Serum 25D level after the summer vs. winter, $P < 0.001$. †Serum 1,25D level after the summer vs. winter, $P < 0.005$.

been reported in the general population and in ESRD patients [21]. We therefore attempted to determine the prevalence of vitamin D deficiency according to the season in a cohort of HD patients. Moreover, we investigated the relationship between serum vitamin D levels and vascular calcification in this population with a consideration of seasonal variations in vitamin D levels.

2. Subjects and methods

2.1. Study design

This is a prospective, observational, single-center cohort study of prevalent patients treated with HD. First, we investigated the seasonal variation in serum 25D levels and the prevalence of vitamin D deficiency in the HD patients. Second, we assessed serum 25D and 1,25-dihydroxyvitamin D (1,25D) levels at the end of the summer (September) and winter (March) to investigate the relationship among serum vitamin D levels, vascular calcification, and other biochemical factors according to the season.

2.2. Subjects

We analyzed 289 HD patients visiting our HD unit at Gachon University Gil Hospital between January 2009 and December 2010. Patients were enrolled in the study: if they (i) had been on HD for at least 3 months; (ii) agreed to participate in the study, which was approved by our Institutional Review Board; and (iii) were free of any complicating conditions that affect serum 25D levels, such as an underlying malignancy, active liver disease or infection.

2.3. Biochemical analysis

Blood pressure (BP) was evaluated just prior to mid-week HD sessions, from which blood chemistry analyses were obtained. Predialysis BP was measured by trained health care professionals or automated monitors, with the patient in a supine position for 5 min prior to measuring BP. The upper arm opposite the access side was used. Intact parathyroid hormone (iPTH) was determined by using chemiluminescent immunoassay (ADVIA Centaur® XP, Siemens, Germany). Serum 25D levels were determined using a chemiluminescent immunoassay (LIAISON® 25 OH Vitamin D TOTAL Assay, DiaSorin Inc., Stillwater, MN, USA). 25D measures between 4.0 and 150 ng/ml which is based on an inter-assay precision that approximates 20% coefficient of variation (CV). Serum 1,25D levels were determined via a radioimmunoassay (IDS, ^{125}I RIA Kit, Diasorin Inc., Stillwater, MN, USA). The reportable range of 1,25D assay is 2.9–210 pg/ml and inter-assay precision is below 14% CV. Based on previous reports, we classified vitamin D deficiency as serum 25D levels lower than 15 ng/ml, vitamin D insufficiency as levels between 16 and 30 ng/ml and adequate vitamin D levels as levels higher than 30 ng/ml [22].

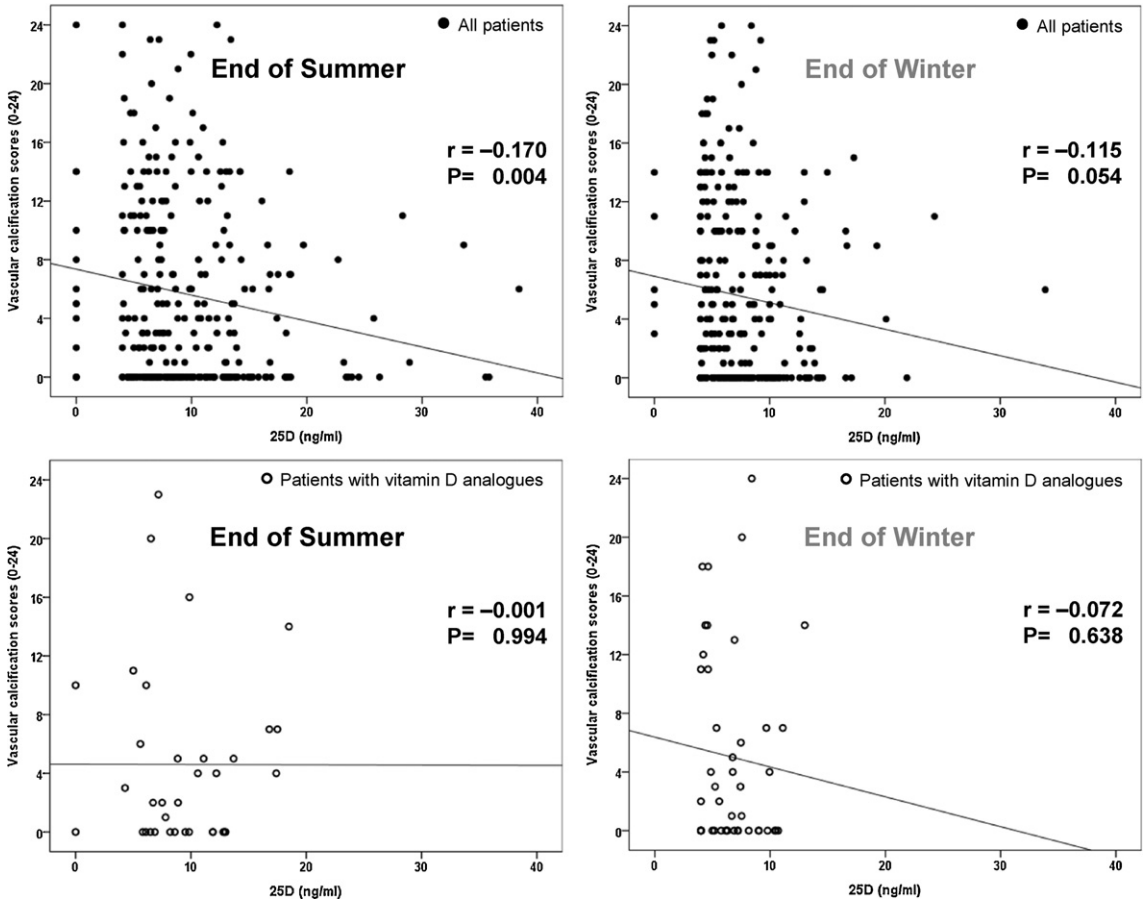

Fig. 2. Correlation between serum 25D levels and vascular calcification scores according to season.

The parameters examined included age, BP, body mass index, the duration of dialysis (months), dialysate calcium concentration, single pool Kt/V (spKt/V), smoking status, previous CVD history and medication history. Other parameters that were measured, using standard laboratory techniques, included hemoglobin, calcium, phosphorus, iPTH, total cholesterol (TC), triglyceride (TG), albumin, and highly sensitive C-reactive protein (hs-CRP) levels.

2.4. Vascular calcification scores

Vascular calcifications were evaluated by a single observer blind to the clinical data based on a lateral lumbar spine X-ray using the semiquantitative scores described by Kauppila et al. [5]. Briefly, a semiquantitative scoring system was used to assess calcifications in the anterior and posterior aortic walls as observed in four image segments corresponding to the areas in front of each of the first four lumbar vertebrae. Each segment was assigned a score for anterior wall calcifications and a score for posterior wall calcifications. The scores ranged between 0 and 3 (0 = no calcification, 1 = irregular punctate calcifications, 2 = localized linear calcifications, and 3 = linear calcifications spanning the length of the vertebra). The total score of a patient was calculated as the sum of the partial scores and ranged from 0 to 24. Kauppila scores > 7 have been associated with higher coronary calcification as evaluated by electron beam computed tomography, a technique with high sensitivity and specificity [23].

2.5. Statistical analysis

Continuous variables were tested for normality using the Kolmogorov–Smirnov test before further statistical analysis. Variables were expressed as frequencies for categorical variables and means ± standard deviation for normally distributed variables. Comparisons between groups were performed using the unpaired Student's *t*-test, paired *t*-test or Chi-square test depending on variable characteristics. The Spearman correlation was used for univariate analysis. Multivariate analysis consisted of a binary logistic regression (confidence interval of 95%) performed between Kauppila scores > 7 and ≤7 as dependent variables. $P < 0.05$ was considered statistically significant for all analysis. SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

3. Results

The clinical characteristics of the 289 HD patients are shown in Table 1. The mean age was 56.9 ± 13.7 years, and the median time on HD was 25 (interquartile range of 9–60) months. The mean serum 25D concentration was 9.8 ± 6.1 ng/ml, and the mean 1,25D level was 8.5 ± 4.5 pg/ml. Kauppila scores revealed 180 patients (62.3%) with vascular calcification and higher VCS was >7 for 91 patients (31.5%).

3.1. Seasonal variation in serum 25D levels and prevalence of vitamin D deficiency in HD patients

The vitamin D levels showed marked seasonal variation. At the end of summer, the 25D and 1,25D levels were 10.4 ± 5.7 ng/ml and 9.1 ± 4.1 pg/ml. These levels decreased to 7.9 ± 3.8 ng/ml ($P < 0.001$) and 8.2 ± 6.9 pg/ml ($P < 0.019$), respectively, at the end of the winter (Fig. 1(A)). The results were similar whether the analysis was performed for the whole group or after excluding patients with

Table 1
Characteristics of patients at inclusion.

Variable	Mean ± SD (n = 289)
Age (year)	56.9 ± 13.7
Gender (male %)	49.5
Diabetes (%)	46.4
Cardiovascular	
Body mass index (kg/m^2)	20.8 ± 6.2
Previous CVD (%)	34.9
Smoking habit (%)	39.1
Blood pressure (mmHg)	
Systolic	149.0 ± 26.2
Diastolic	74.0 ± 15.4
Antihypertensive drugs (%)	
RAS blockades	48.1
Beta-blockers	43.9
CCB	45.0
Anti-platelet agents (%)	89.3
Statins (%)	20.4
Calcium based phosphate binder (%)	58.8
Vitamin D analogue (%)	12.5
HD	
Dialysis duration (months)[a]	25 (9–60)
spKt/V	1.4 ± 0.5
Dialysate calcium concentration (mmol/l)	1.6 ± 0.2
Laboratory	
TC (mg/dl)	151.0 ± 35.7
LDL-C (mg/dl)	82.8 ± 30.9
TG (mg/dl)	117.8 ± 76.5
Albumin (g/l)	3.8 ± 0.4
Hemoglobin (g/dl)	10.6 ± 1.3
Calcium (mg/dl)	8.2 ± 0.8
Phosphorus (mg/dl)	5.0 ± 1.6
Intact PTH (pg/ml)	182.7 ± 247.4
hsCRP (mg/dl)	0.8 ± 1.5
25D (ng/ml)	9.8 ± 6.1
Deficiency (≤15 ng/ml, %)	86.2
Insufficiency (16–30 ng/ml, %)	10.7
Normal (>30 ng/ml, %)	3.1
1,25D (pg/ml)	8.5 ± 4.5
Kauppila index	5.6 ± 6.3
Higher VCS (>7, %)	31.5

CVD, cardiovascular disease; RAS, renin–angiotensin system; CCB, calcium channel blocker; HD, hemodialysis; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TG, triglyceride; PTH, parathyroid hormone; hsCRP, highly sensitive C-reactive protein; 25D, 25-hydroxyvitamin D; 1,25D, 1,25-dihydroxyvitamin D; VCS, vascular calcification score.
[a] Median, interquartile range.

vitamin D analogues (Fig. 1(B)). At the end of the summer, only 3.1% of patients had adequate levels of 25D, 10.7% had insufficient levels and 86.2% had deficient levels (Table 1). The prevalence of vitamin D deficiency increased to 96.2% (P < 0.001) at the end of the winter (Fig. 1(C)). Female gender and diabetes were associated with vitamin D deficiency (Table 2).

3.2. Association of serum 25D levels with vascular calcification

Analysis with Spearman's correlation coefficient revealed inverse correlations between 25D serum levels and VCS (r = −0.170, P = 0.004) at the end of the summer, but not at the end of the winter (r = −0.114, P = 0.054; Fig. 2). Therefore, we analyzed the data to reveal the association of serum 25D level with vascular calcification at the end of the summer, when vitamin D levels were found to peak.

Table 2
Multiple logistic regression analysis of factors associated with 25D deficiency at the end of summer.

Parameters	Odds ratio	95% CI	P
Dependent variable: 25D ≤15 ng/ml			
Female gender	3.892	1.678–9.025	**0.002**
Diabetes	2.832	1.190–6.739	**0.019**
Age	1.018	0.987–1.050	0.261
Kauppila index	1.042	0.960–1.131	0.322
Dialysis duration	1.002	0.994–1.010	0.688

Bold values means statistical significance (P < 0.05).

Table 3 compares the epidemiological, clinical and laboratory results of patients with Kauppila scores > 7 and ≤7. Patients with higher VCSs were older and had a higher prevalence of diabetes and history of CVD, higher levels of BP, TC, and LDL cholesterol and lower levels of albumin, iPTH, and 25D. We found no difference between groups, in the proportion of patients treated with vitamin D analogues or calcium-based phosphate binders.

Table 4 shows the relationship between vascular calcification estimated with Kauppila scores and related factors. The 25D levels were inversely related to vascular calcification in univariate analysis (r = −0.170, P = 0.004; Fig. 2). However, after correction for confounding factors such as age, systolic BP, LDL cholesterol, diabetes, previous CVD and albumin, this relation lost statistical significance. Multivariate analysis showed that age, systolic BP, and LDL-cholesterol levels were directly associated with higher VCSs (Table 4). After excluding patients with vitamin D analogues, an analysis equivalent to that performed with the whole group yielded similar results: univariate analysis comparing patients with Kauppila scores > 7 or ≤7 yielded significant differences for age, diabetes, BP, TC,LDL cholesterol, albumin and 25D. Based on multivariate analysis, the independent predictors of Kauppila scores > 7 are age (P < 0.001), systolic BP (P = 0.040) and LDL-cholesterol levels (P = 0.031; Supplementary Table S1).

4. Discussion

In agreement with previous studies, vitamin D deficiency and insufficiency were highly prevalent in the HD patients in our study, with levels tending to be lower in women and patients with diabetes. The vast majority of our patients showed very low levels of 25D, but the 25D levels were similar to those of previous studies in Korea [24,25]. Vitamin D deficiency is very common in dialysis populations, even in countries that receive relatively high levels of sunlight [26,27]. Female patients were most likely to have lower levels due to reduced sun exposure. Further, diabetes may predispose individuals to an even greater risk of vitamin D deficiency due to bowel motility disturbances, fat malabsorption and an association with celiac disease [28].

Marked seasonal variations in Vitamin D levels were observed. In a previous study [21], seasonal variations in 25D levels were reported in ESRD patients. Our dialysis center is located at a latitude of 37°N in Incheon, Korea, with the four distinct seasons typical of the temperate zone including very wide ranges of temperature and humidity. During the winter, at north or south latitudes above 35°, very little, if any, vitamin D can be produced in the skin. Additionally, ESRD patients have dietary and social restrictions limiting their acquisition of vitamin D.

Vitamin D is related to both skeletal and non-skeletal health outcomes such as CVD, diabetes mellitus, cancer, and immune dysfunction. Vitamin D deficiency has been reported to increase cardiovascular morbidity and mortality both in the general population and in chronic kidney disease (CKD) patients [29,30]. The potential ameliorating effects of vitamin D on CVD include mechanisms related to the development of vascular calcification and atherosclerosis [9]. The role of vitamin D in the development of vascular calcification is still controversial. In our study, 25D levels were inversely related to vascular calcification in the univariate analysis, but after adjusting for confounding factors, 25D serum concentrations were not associated with vascular calcification in HD patients. Similarly, London et al. observed that 1,25D and 25D levels in adult HD patients are negatively correlated with aortic stiffness but not

Table 3
Relationship between vascular calcification and clinical and laboratory parameters.

Variable	All patients			Excluding patients with vitamin D analogues		
	≤7 (*n* = 198)	>7 (*n* = 91)	*P*	≤7 (*n* = 170)	>7 (*n* = 84)	*P*
Age (years)	53.4 ± 13.5	64.2 ± 11.2	**<0.001**	52.8 ± 13.0	64.2 ± 11.2	**<0.001**
Gender (male %)	44.7	41.8	0.066	56.8	41.7	**0.025**
Diabetes (%)	40.5	58.2	**0.004**	42.0	59.5	**0.007**
Cardiovascular						
Body mass index (kg/m^2)	21.6 ± 6.1	20.7 ± 5.6	0.251	20.6 ± 6.0	21.5 ± 5.7	0.252
Previous CVD (%)	31.1	42.9	**0.046**	29.6	41.7	0.053
Smoking habit (%)	40.0	39.6	0.999	42.0	39.3	0.929
Blood pressure (mmHg)						
Systolic	146.3 ± 25.6	154.9 ± 26.7	**0.016**	146.3 ± 26.2	154.4 ± 26.3	**0.029**
Diastolic	76.2 ± 15.7	69.5 ± 14.0	**0.001**	75.9 ± 16.0	69.6 ± 14.1	**0.004**
Antihypertensive (%)						
RAS blockade (%)	51.1	41.8	0.144	51.2	44.0	0.285
Beta-blocker (%)	43.7	45.1	0.829	45.1	47.6	0.703
CCB (%)	44.7	45.1	0.960	45.7	44.0	0.807
Antiplatelet agents (%)	92.1	86.8	0.159	91.4	85.7	0.172
Statin (%)	21.1	18.7	0.644	21.0	19.0	0.720
Calcium-based phosphate binder (%)	60.5	57.1	0.589	59.9	54.8	0.441
Vitamin D analogue (%)	14.7	7.7	0.094			
HD						
Dialysis duration (months)	39.6 ± 45.1	46.9 ± 49.0	0.234	38.0 ± 43.7	44.1 ± 46.8	0.330
spKt/V	1.4 ± 0.5	1.4 ± 0.3	0.377	1.3 ± 0.3	1.4 ± 0.3	0.056
Dialysate calcium concentration (mmol/l)	1.6 ± 0.2	1.5 ± 0.2	0.059	1.6 ± 0.2	1.5 ± 0.2	0.056
Laboratory						
TC (mg/dl)	147.7 ± 34.7	158.6 ± 37.0	**0.022**	147.5 ± 35.1	157.7 ± 35.6	**0.039**
LDL-C (mg/dl)	79.0 ± 29.8	91.3 ± 31.8	**0.003**	78.3 ± 30.0	90.4 ± 31.8	**0.005**
TG (mg/dl)	120.2 ± 83.9	114.0 ± 58.4	0.538	124.4 ± 87.8	111.3 ± 54.0	0.233
Albumin (mg/dl)	3.9 ± 0.4	3.8 ± 0.3	**0.031**	3.9 ± 0.4	3.8 ± 0.3	**0.024**
Hemoglobin (g/dl)	10.7 ± 1.4	10.7 ± 1.1	0.861	10.7 ± 1.4	10.7 ± 1.0	0.236
Calcium (mg/dl)	8.2 ± 0.8	8.3 ± 0.8	0.437	8.2 ± 0.8	8.2 ± 0.7	0.915
Phosphorus (mg/dl)	4.9 ± 1.6	5.1 ± 1.6	0.416	4.9 ± 1.6	5.1 ± 1.7	0.417
iPTH (pg/dl)	197.9 ± 272.7	142.3 ± 160.6	**0.043**	147.7 ± 239.3	114.3 ± 112.4	0.249
hsCRP (mg/dl)	0.4 ± 0.6	0.6 ± 1.1	0.255	0.3 ± 0.6	0.7 ± 1.3	0.393
25D (ng/ml)	10.5 ± 6.2	8.7 ± 5.4	**0.021**	10.6 ± 6.5	8.8 ± 5.5	**0.031**
1,25D(pg/ml)	9.0 ± 4.5	8.0 ± 4.2	0.106	8.7 ± 4.3	7.8 ± 3.4	0.068

Bold values means statistical significance ($P < 0.05$).
CVD, cardiovascular disease; RAS, renin–angiotensin system; CCB, calcium channel blocker; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TG, triglyceride; PTH, parathyroid hormone; hsCRP, highly sensitive C-reactive protein; 25D, 25-hydroxyvitamin D; 1,25D, 1,25-dihydroxyvitamin D.

with vascular calcification [20]. Shroff et al. reported a bimodal association between vascular calcification and 1,25D levels in dialyzed children, but no association between 25D levels and vascular measurements [19]. On the contrary, lower levels of 25D are a cardiovascular risk marker in HD patients of their strong association with higher brain natriuretic peptide (BNP) levels, increased pulse pressure and presence of vascular calcifications [27]. In their study, the population was relatively old with long dialysis duration, and high serum calcium.

In pre-dialysis patients, the relationships between 25D levels and vascular calcification are also controversial. Recently, Barreto et al. showed that there is no association between 25D levels and aortic calcification in CKD patients [18]. On the other hand, studies have shown an independent and negative association between serum levels of 25D and vascular calcification in non-dialysis patients with CKD stages 4 and 5 [31]. In their study, 25D deficiency appeared to be less severe but vascular calcification was more frequent. Vitamin D (25D) deficiency is very common even in the general Korean population [32]. The high prevalence of 25D deficiency may be related to genetic reasons or environmental factors. The high frequency of vascular calcification may be explained by different characteristics of the study population. In their study, the population was relatively old and had high diabetic patients.

Like clinical studies, recent *in vivo* genetic mouse studies have provided insights into vitamin D-dependent and vitamin D-independent vascular calcification [33]. There are a lot of known inducers and inhibitors of vascular calcification. For instance, fibroblast growth factor 23 (FGF23)–klotho system in the regulation of calcium and phosphate balance is important. Genetic inactivation of either *Fgf23* or *klotho* leads to increased serum Ca, P and 1,25D levels in these mutant mice; such abnormal mineral ion and vitamin D homeostasis in *Fgf23*- and *klotho*-knockout mice is associated with widespread soft tissue and vascular calcifications [30,34]. Conversely, lowered serum P levels in *klotho*-knockout mice reduce vascular calcification, despite the presence of significantly higher serum Ca and 1,25D levels [35,36]. This study provides *in vivo* evidence of the beneficial effects of reduced serum P levels in preventing vascular calcification, even in the presence of extremely high serum 1,25D levels.

We have shown that the analyzed clinical and epidemiological variables reveal an association between vascular calcifications and age, systolic BP, and LDL-cholesterol levels. This finding agrees with other published studies, where calcifications are generally related to age, diabetes, arterial hypertension, dialysis duration, CVD, and hyperlipidemia [31,37].

Table 4
Multiple logistic regression analysis of factors associated with higher vascular calcification scores.

Parameters	Odds ratio	95% CI	*P*
Dependent variable: Kaupilla >7			
Age	1.068	1.041–1.095	**<0.001**
SBP	1.014	1.002–1.026	**0.021**
LDL-C	1.012	1.001–1.023	**0.031**
25D	0.974	0.920–1.031	0.370

Bold values means statistical significance ($P < 0.05$).
SBP, systolic BP; LDL-C, LDL-cholesterol; 25D, 25-hydroxyvitamin D.

In conclusion, vitamin D deficiency and insufficiency were highly prevalent in the HD patients studied, with marked seasonal variation. However, low 25D levels could not be identified as an independent predictor of vascular calcification in these patients. Vascular calcification is a complex, ectopic biomineralization process, involving autocrine, paracrine and endocrine interactions of numerous factors. Therefore, the association between vitamin D levels and vascular calcification cannot easily be explained as a cause–effect relationship because vitamin D deficiency results from many calcification-promoting and -suppressing factors. Larger-scale longitudinal multicenter studies and experimental studies are needed to confirm our results and to elucidate the role of vitamin D deficiency in HD patients.

Conflicts of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.11.028.

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