

25-hydroxyvitamin D Levels was not Associated with Blood Pressure and Arterial Stiffness in Patients with Chronic Kidney Disease

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Background: We investigated the effect of vitamin D deficiency on cardiovascular risk profiles in an Asian population with chronic kidney disease (CKD).

Methods: A total of 210 participants (62 non-dialysis CKD patients and 148 hemodialysis [HD] patients) were enrolled between December 2009 and February 2010. Vitamin D deficiency was determined using the serum 25-hydroxyvitamin D [25(OH)D] concentration. Blood pressure and arterial stiffness were measured. Subjects were divided into groups according to 25(OH)D concentration based on a cut-off of 13.5 ng/mL in non-dialysis CKD patients and 11.3 ng/mL in HD patients.

Results: The mean age was 61.7±12.3 years in non-dialysis CKD patients and 57.0±12.7 years in HD patients. In the non-dialysis CKD group, mean estimated glomerular filtration rate (eGFR) was 29.7±15.4 mL/min/1.73 m². Mean 25(OH)D concentration was 13.6±7.8 ng/mL in non-dialysis CKD patients and 11.3±6.7 ng/mL in HD patients. More than half of the subjects had vitamin D deficiency (67.6% in non-dialysis CKD patients and 80.4% in HD patients). There were no significant differences in systolic blood pressure, pulse pressure, and arterial stiffness between higher and lower 25(OH)D groups among non-dialysis CKD and HD patients. Multivariate analysis revealed that female sex (odds ratio [OR]: 5.890; 95% confidence interval [CI]: 2.597-13.387; p<0.001) and presence of diabetes (OR: 2.434; 95% CI: 1.103- 5.370; p=0.028) were significantly associated with lower serum 25(OH)D levels in HD patients.

Conclusion: The prevalence of vitamin D deficiency was high in both non-dialysis CKD patients and HD patients. Serum 25(OH)D concentration was not a significant factor associated with blood pressure and arterial stiffness among non-dialysis CKD and HD patients.

Key Words: Blood pressure, Cardiovascular risk, Chronic kidney disease, 25-Hydroxyvitamin D

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Introduction

Vitamin D is an essential nutrient with pleiotropic effects involving the kidneys^{1,2}, cardiovascular system^{3,4}, im-

mune system⁵, and mineral-bone metabolism⁶, and is also involved in cancer⁷. Vitamin D levels are also associated with the glomerular filtration rate (GFR)⁸, and vitamin D deficiency is correlated with a rapid decline in GFR².

Therefore, in chronic kidney disease (CKD), many patients have insufficiency or deficiency of vitamin D^{9,10}. Vitamin D deficiency is significantly associated with adverse clinical outcomes in CKD and dialysis patients^{2,10-12}. Patients with low 25-hydroxyvitamin D [25(OH)D] levels had higher all-cause mortality² and higher risk of hospitalization¹². Furthermore, peritoneal dialysis patients with a lower 25(OH)D concentration showed a significantly greater risk of fatal or nonfatal cardiovascular events¹⁰. Because cardiovascular disease is the most common cause of death in CKD patients¹³, evaluating the association between vitamin D deficiency and cardiovascular risk has clinical relevance.

Many previous observational studies have suggested the effect of vitamin D deficiency on adverse cardiovascular outcomes. Few studies have assessed vitamin D concentration and specific cardiovascular risk profiles in CKD patients. Furthermore, most studies have been confined to Western populations. Because of the differences in region, climate, nutritional status, and clinical practice patterns, we sought to investigate the effect of vitamin D deficiency on cardiovascular risk profiles in an Asian population with CKD. Therefore, in the current study, we measured the relationship of serum 25(OH)D with blood pressure and arterial stiffness in Korean patients with non-dialysis CKD and chronic hemodialysis (HD).

Materials and Methods

1. Subjects

This study is part of a larger study investigating the effect of low vitamin D levels on clinical outcomes¹². We screened and recruited non-dialysis CKD and chronic HD patients between December 2009 and February 2010 at CHA Bundang Medical Center. CKD stage was determined according to the Kidney Disease Outcomes Quality Initiative guidelines¹⁴. Estimated glomerular filtration rate (eGFR) was calculated using the equation of the Modification of Diet in Renal Disease Study Group¹⁵. Non-dialysis CKD patients included those with two previous, consecutive eGFR measurements of less than 60 mL/min/1.73 m² at an interval of 3-6 months. Chronic HD patients were those

who underwent regular HD treatment for at least three months on a schedule of three times per week (>12 hours/week). We excluded subjects who were <20 or >90 years of age or had an acute infectious disease, unstable vital signs, malignancy, or a prior history of kidney transplantation. Patients were also excluded if they were on active vitamin D supplements, vitamin D analogs, warfarin, steroids, or anticonvulsants within the 6 months prior to study enrollment. A total of 210 participants (62 non-dialysis CKD patients and 148 HD patients) were finally enrolled and analyzed in this study. This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of CHA Bundang Medical Center. Written consent was acquired from all participants.

2. Demographic and biochemical data collection

Demographic and biochemical data were collected at study entry. Age, sex, presence of diabetes and previous cardiovascular disease, and use of medication for renin-angiotensin system blockade, lipid lowering therapy, and calcium-based phosphate binders were recorded. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Blood samples were obtained before the hemodynamic study. In HD patients, blood sampling was done during the predialysis period. Biochemical variables, including white blood cell count, hemoglobin, albumin, blood urea nitrogen, calcium, phosphorous, intact parathyroid hormone (PTH; iPTH), high-sensitivity C-reactive protein (hs-CRP), 25-hydroxyvitamin D₂+D₃, and 1,25-(OH)₂ vitamin D₃, were measured. Serum calcium was adjusted for serum albumin. iPTH levels were evaluated by electrochemiluminescence immunoassay. Serum 25(OH)D concentrations were measured using a chemiluminescent immunoassay (LIAISON; DiaSorin Inc., Saluggia, Italy). Levels of 1,25-(OH)₂D were determined using a ¹²⁵I radioimmunoassay (DiaSorin Inc.).

3. Measurement of cardiovascular risk profiles

Before measurement of cardiovascular risk profiles, participants were instructed to avoid exercise, caffeine, high-fat foods, or tobacco for at least 12 hours. Blood pressure was measured three times after 15 minutes of recumbency. The average value of three measurements was utili-

zed for data analysis. Pulse pressure was calculated using the following formula: pulse pressure = systolic blood pressure – diastolic blood pressure. Arterial stiffness was determined using brachial-ankle pulse wave velocity (baPWV) with a commercially available device (VP-2000; Colin, Komaki, Japan). After 15 minutes of recumbency, pulse wave forms were obtained from the brachial and posterior tibial artery¹⁶. Pulse wave velocity was calculated as the distance between two arterial recording sites divided by transit time, as described previously¹⁷. In non-dialysis CKD patients, the mean baPWV of the right and left sides was used. A single value of baPWV from one arm without arteriovenous access was used for analysis in the HD group. Blood pressure and arterial stiffness measurements were conducted by a single practitioner who was blinded to clinical information.

4. Statistical analysis

Continuous variables are expressed as mean±standard deviation and categorical variables as a number (percentage). Based on previous studies¹⁴, vitamin D deficiency was defined as serum 25(OH)D levels <15 ng/mL and vitamin D insufficiency was defined as serum 25(OH)D levels of 15–30 ng/mL. To compare baseline characteristics and cardiovascular risk profiles according to 25(OH)D concentrations, subjects were divided into a higher and a lower 25(OH)D group. The average 25(OH)D concentrations were 13.5 ng/mL in non-dialysis CKD patients and 11.3 ng/mL in HD patients. To compare clinical data and cardiovascular risk profiles, Student's *t*-tests were performed for continuous variables and chi-square tests were performed for categorical variables. Pearson's correlation coefficients were used to assess the relationship between the serum 25(OH)D level and 1,25-(OH)₂D level. We performed binary logistic regression analysis to investigate the effects of covariates on serum 25(OH)D in HD patients. A *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS for Windows (version 18.0; SPSS Inc., Chicago, IL, USA).

Results

1. Baseline characteristics and the prevalence of vitamin D deficiency

Sixty-two non-dialysis CKD subjects and 148 HD subjects were assessed. Baseline characteristics are shown in Table 1. The mean age of the non-dialysis CKD patients was 61.7±12.3 years and that of the HD patients was 57.0±12.7 years. Among the non-dialysis CKD patients, 39 (62.5%) were men; 71 (52.0%) of the HD patients were men. The prevalence rates of diabetes and previous cardiovascular disease were 50.0% and 21.9%, respectively, in the non-dialysis CKD group and 48.6% and 39.9%, respectively, in the HD group. In the non-dialysis CKD group, mean eGFR was 29.7±15.4 mL/min/1.73 m². Mean Kt/V urea was 1.4±0.4 in the HD group. Mean systolic and diastolic blood pressures were 135.6±20.2 and 55.8±13.4 mmHg in the non-dialysis CKD and 145.3±25.2 and 62.6±16.6 mmHg in the HD group, respectively. In addition, the mean baPWV of non-dialysis CKD and HD patients was 17.3±4.5 and 18.4±4.3 m/s, respectively. The mean 25(OH)D concentrations were 13.6±7.8 ng/mL in the non-dialysis CKD patients and 11.3±6.7 ng/mL in the HD patients. Most of the patients had vitamin D deficiency (67.6% of non-dialysis CKD patients and 80.4% of HD patients, respectively) and only a small proportion had adequate vitamin D levels (3.2% of non-dialysis CKD patients and 2.0% of HD patients). Analysis using Pearson's correlation coefficient revealed a direct association between the serum 25(OH)D level and 1,25-(OH)₂D level in the non-dialysis CKD patients (*r*=0.458, *p*<0.001; Fig. 1A), but there was no significant correlation between the serum 25(OH)D level and 1,25-(OH)₂D level in the HD patients (*r*=0.138, *p*=0.138; Fig. 1B).

2. Comparison of clinical characteristics according to serum 25(OH)D levels

When subjects were divided into higher and lower 25(OH)D groups (Table 2), the proportion of men was significantly higher in the higher 25(OH)D group in both non-dialysis CKD and HD patients (79.2%, *p*=0.048 and 78.8%, *p*<0.001, respectively). In contrast, the proportion of diabetes was significantly greater in the lower 25

(OH)D group in the HD patients (56.3%, $p=0.009$). In the non-dialysis CKD patients, lower eGFR (20.4 ± 9.7 vs 37.5 ± 15.0 , $p<0.001$, respectively) was observed in the lower 25(OH)D group, accompanied by significantly lower hemoglobin but higher phosphorous and iPTH concentrations compared to those in the higher 25(OH)D group (Table 2). This suggested that the decreased uptake of

25(OH)D by impaired kidneys may contribute to vitamin D deficiency or insufficiency in non-dialysis CKD patients¹⁸. In the lower 25(OH)D group, significantly decreased serum albumin levels and higher hs-CRP levels were observed among non-dialysis CKD patients (Table 2). In HD patients, albumin levels and the use of calcium-based phosphate binders were significantly lower in the lower 25(OH)

Table 1. Baseline characteristics of subjects

	Non-dialysis CKD patients	HD patients	p-value
Number (%)	62 (29.5)	148 (70.5)	-
Age (years)	61.7 \pm 12.3	57.0 \pm 12.7	0.014
Men (%)	62.5	52.0	0.128
Diabetes (%)	50.0	48.6	0.763
BMI (kg/m ²)	24.2 \pm 3.3	24.4 \pm 3.6	<0.001
Previous CVD (%)	21.9	39.9	0.018
Coronary artery disease	4.3	18.2	0.004
Cerebrovascular attack	17.2	27.0	0.163
Peripheral artery disease	4.3	12.2	0.133
eGFR (mL/min/1.73 m ²)	29.7 \pm 15.4	-	-
Kt/Vurea	-	1.4 \pm 0.4	-
WBC (10 ³ / μ L)	6.3 \pm 2.0	6.3 \pm 2.0	0.838
Hemoglobin (g/dL)	11.5 \pm 1.6	10.5 \pm 2.7	0.010
Albumin (mg/dL)	4.2 \pm 0.4	3.9 \pm 0.4	<0.001
BUN (mg/dL)	37.8 \pm 19.8	63.9 \pm 21.1	<0.001
Calcium (mg/dL)	9.1 \pm 0.6	9.2 \pm 0.9	0.578
Phosphorous (mg/dL)	3.5 \pm 0.7	4.8 \pm 1.7	<0.001
iPTH (pg/dL)	96.8 \pm 123.9	178.6 \pm 252.3	0.002
CRP (mg/dL)	0.2 \pm 0.4	0.5 \pm 1.5	0.031
Medications			
ACEi/ARBs (%)	85.2	84.0	0.854
Statin (%)	48.4	45.3	0.650
Ca based P-binder (%)	14.1	73.0	<0.001
SBP (mmHg)	135.6 \pm 20.2	145.3 \pm 25.2	0.005
PP (mmHg)	55.8 \pm 13.4	62.6 \pm 16.6	0.003
BaPWV (m/s)	17.3 \pm 4.5	18.4 \pm 4.3	0.108
1,25-(OH) ₂ D (ng/mL)	31.1 \pm 13.9	22.5 \pm 8.5	<0.001
25(OH)D (ng/mL)	13.6 \pm 7.8	11.3 \pm 6.7	0.049
Status of 25(OH)D [14]			0.061
Normal (>30 ng/mL, %)	2 (3.2)	3 (2.0)	
Insufficiency (15-30 ng/mL, %)	18 (29.0)	26 (17.6)	
Deficiency (<15 ng/mL, %)	42 (67.6)	119 (80.4)	

Data are presented as means \pm SD or number of observations (%).

Abbreviations: 1,25-(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BUN, blood urea nitrogen; Ca-based P-binder, calcium-based phosphate binder; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; PP, pulse pressure; SBP, systolic blood pressure; WBC, white blood cell.

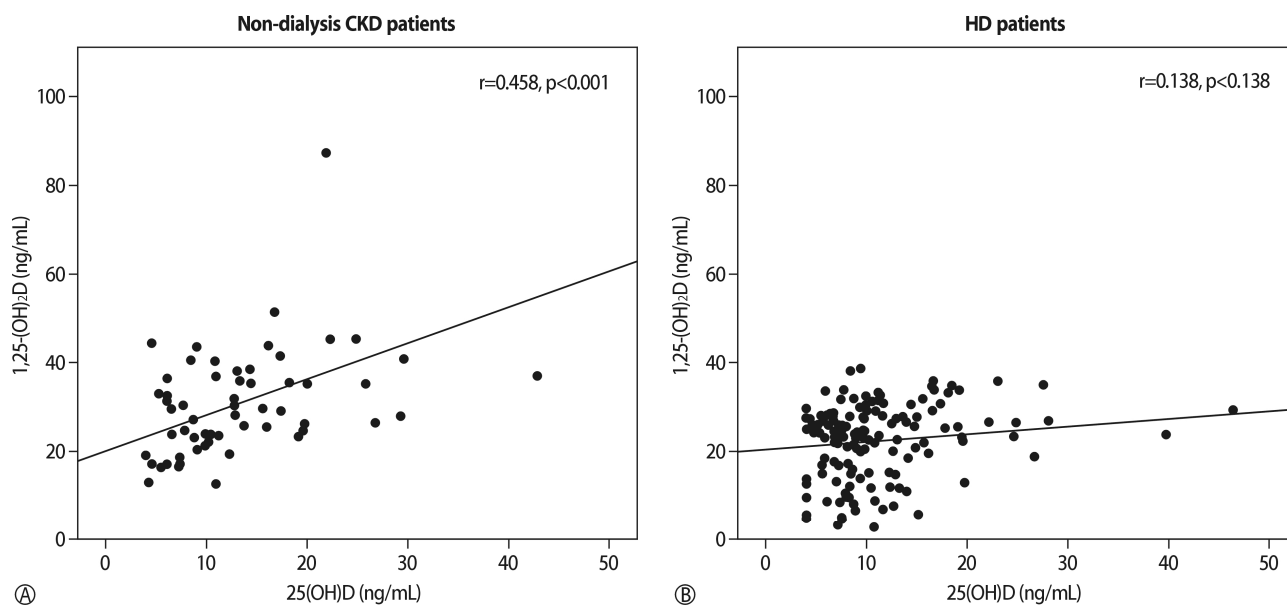


Fig. 1. Pearson's correlation coefficient (R) and p-value (P) for 1,25-(OH)₂D and 25(OH)D. (A) Scatter plot of 1,25-(OH)₂D and 25(OH)D in non-dialysis CKD patients and (B) HD patients. CKD, chronic kidney disease; HD, hemodialysis.

D group (Table 2).

In non-dialysis CKD patients, systolic blood pressure (137.8 ± 18.8 vs. 131.9 ± 22.3 mmHg, $p=0.276$), pulse pressure (57.1 ± 12.5 vs. 52.9 ± 14.5 mmHg, $p=0.198$) and baPWV (17.6 ± 4.7 vs. 17.0 ± 4.1 m/s, $p=0.639$) were slightly higher in the lower 25(OH)D group, but there was no statistical significance (Table 2). Systolic blood pressure, pulse pressure, and baPWV showed no trend or statistical significance in a comparison between HD patients with higher and lower 25(OH)D (Table 2).

3. Factors associated with lower serum 25(OH)D levels in HD patients

In univariate analysis, female sex (odds ratio [OR]: 6.212; 95% confidence interval [CI]: 2.838-13.597; $p<0.001$), presence of diabetes (OR: 2.429; 95% CI: 1.207-4.887; $p=0.013$), and BMI (OR: 0.889; 95% CI: 0.798-0.991; $p=0.034$) were found to be independent predictors of serum 25(OH)D <11.3 ng/mL in HD patients (Table 3). However, multivariate logistic analysis revealed that only female sex (OR: 5.890; 95% CI: 2.597-13.387; $p<0.001$) and presence of diabetes (OR: 2.434; 95% CI: 1.103-5.370; $p=0.028$) were significantly associated with lower serum 25(OH)D levels (<11.3 ng/mL) in HD patients (Table 3).

Discussion

This study showed that the prevalence of vitamin D deficiency was high in both non-dialysis CKD patients and HD patients. More than half of subjects had vitamin D deficiency and less than 5% of the subjects had adequate vitamin D levels. Our study also demonstrated that cardiovascular risk was greater in the lower serum 25(OH)D group among non-dialysis CKD patients. The lower serum 25(OH)D group among non-dialysis CKD patients also had higher values for systolic blood pressure, pulse pressure, and baPWV, but there was no statistical significance. We did not find significant differences in cardiovascular risk profiles among HD patients according to the serum 25(OH)D level.

The association between vitamin D and blood pressure has been thoroughly investigated in the general population. Several observational studies^{19,20} and cross-sectional studies²¹⁻²⁵ demonstrated that vitamin D had a significant association with hypertension. In a study using data from the Korea National Health and Nutrition Examination Survey, 25(OH)D showed inverse correlations with systolic and diastolic blood pressure, while serum PTH levels showed positive correlations with systolic and diastolic blood pressure in 4,513 participants not taking antihy-

pertensive medication²⁴). In the elderly, lower serum 25(OH)D levels were inversely and independently associated with blood pressure in subjects who were over 64 years of age²³. Moreover, Belen et al.²⁵ showed that lower serum 25(OH)D concentrations had an independent relationship with the presence of resistant hypertension. They included 50 subjects with resistant hypertension, 50 with controlled hypertension, and 50 normotensive subjects. Serum 25(OH)D levels were significantly lower in the resistant

hypertensive group compared to the controlled hypertensive and normotensive groups²³. However, there are still conflicting results regarding the association between vitamin D and blood pressure^{26,27}. Randomized trials investigating the effect of vitamin D supplementation on blood pressure have shown equivocal results²⁷. The Women's Health Initiative was a randomized trial that investigated dietary supplementation with calcium plus vitamin D in 36,000 menopausal women with a median follow up dura-

Table 2. Comparison of clinical characteristics based on mean 25(OH)D serum levels

	Non-dialysis CKD patients			HD patients		
	25(OH)D ≥ 13.5 ng/mL	25(OH)D < 13.5 ng/mL	p-value	25(OH)D ≥ 11.3 ng/mL	25(OH)D < 11.3 ng/mL	p-value
Number (%)	24 (38.7)	38 (61.3)	-	52 (35.1)	96 (64.9)	-
25(OH)D (ng/mL)	21.5 ± 6.9	8.8 ± 2.9	<0.001	18.0 ± 7.0	7.7 ± 2.1	<0.001
1,25-(OH) ₂ D (ng/mL)	37.8 ± 17.8	27.0 ± 8.5	<0.001	23.7 ± 8.9	21.9 ± 8.4	0.099
Age (years)	62.3 ± 11.6	61.4 ± 12.5	0.412	56.1 ± 13.0	58.9 ± 11.8	0.071
Men (%)	19 (79.2)	21 (55.3)	0.048	41 (78.8)	36 (37.5)	<0.001
Diabetes (%)	10 (41.7)	22 (57.9)	0.162	18 (34.6)	54 (56.3)	0.009
BMI (kg/m ²)	24.0 ± 2.7	24.4 ± 3.6	0.252	23.0 ± 2.9	21.9 ± 3.3	0.195
Previous CVD (%)	5 (20.8)	9 (23.7)	0.525	23 (44.2)	36 (37.5)	0.266
CAD	1 (4.2)	1 (2.6)	0.628	7 (13.5)	20 (20.8)	0.189
CVA	4 (16.7)	7 (18.4)	0.572	17 (32.7)	23 (24.0)	0.171
PAD	1 (4.2)	2 (5.3)	0.669	5 (9.8)	13 (13.5)	0.354
eGFR (mL/min/1.73 m ²)	37.5 ± 15.0	20.4 ± 9.7	<0.001	-	-	-
WBC (10 ³ /μL)	6.2 ± 1.6	6.4 ± 2.2	0.185	6.2 ± 1.9	6.3 ± 2.1	0.641
Hb (g/dL)	12.3 ± 1.6	11.0 ± 1.3	<0.001	10.3 ± 0.9	10.6 ± 3.2	0.383
Albumin (mg/dL)	4.4 ± 0.3	4.1 ± 0.4	<0.001	4.0 ± 0.3	3.9 ± 0.4	0.020
BUN (mg/dL)	32.8 ± 14.6	40.8 ± 21.6	<0.001	65.3 ± 17.9	63.3 ± 22.6	0.454
Calcium (mg/dL)	9.2 ± 0.4	9.1 ± 0.6	0.052	9.2 ± 0.7	9.2 ± 1.0	0.980
P (mg/dL)	3.5 ± 0.7	3.8 ± 1.0	<0.001	5.0 ± 1.8	4.8 ± 1.8	0.238
iPTH (pg/dL)	59.1 ± 50.1	119.4 ± 146.2	<0.001	170.6 ± 208.0	183.0 ± 273.2	0.693
CRP (mg/dL)	0.2 ± 0.3	0.2 ± 0.4	0.038	0.3 ± 0.6	0.6 ± 1.9	0.115
Medications						
ACEi/ARBs (%)	20 (83.3)	38 (100)	0.061	36 (69.2)	77 (80.2)	0.198
Statin (%)	11 (45.8)	20 (52.6)	0.397	22 (44.0)	45 (47.4)	0.417
Ca based P-binder (%)	4 (16.7)	5 (13.2)	0.487	41 (82.0)	67 (70.5)	0.022
SBP (mmHg)	131.9 ± 22.3	137.8 ± 18.8	0.276	146.0 ± 26.0	143.0 ± 23.8	0.406
PP (mmHg)	52.9 ± 14.5	57.5 ± 12.5	0.198	64.0 ± 16.2	60.2 ± 17.2	0.184
BaPWV (m/s)	17.0 ± 4.1	17.6 ± 4.7	0.639	18.4 ± 4.5	18.5 ± 4.0	0.871

Data are presented as means ± SD or number of observations (%).

Abbreviations: 1,25-(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BUN, blood urea nitrogen; Ca-based P-binder, calcium-based phosphate binder; CAD, coronary artery disease; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iPTH, intact parathyroid hormone; P, phosphate; PAD, peripheral artery disease; PP, pulse pressure; SBP, systolic blood pressure; VD, vascular disease; WBC, white blood cell.

Table 3. Binary logistic regression analysis with 25(OH)D \geq 11.3 or $<$ 11.3 ng/mL among HD patients

Univariate analysis	OR (95% CI)	p-value
Sex (male/female)	6.212 (2.838-13.597)	<0.001
Age (year)	0.982 (0.956-1.010)	0.203
Diabetes (absent/present)	2.429 (1.207-4.887)	0.013
Previous CVD (absent/present)	0.757 (0.381-1.502)	0.425
BMI (kg/m ²)	0.889 (0.798-0.991)	0.034
P (mg/dL)	0.920 (0.757-1.119)	0.404
Albumin (mg/dL)	0.428 (0.154-1.190)	0.104
Ca based P-binder (nonuser/user)	0.525 (0.225-1.190)	0.136
Multivariate analysis	OR (95% CI)	p-value
Sex (male/female)	5.890 (2.597-13.387)	<0.001
Age (year)	0.974 (0.944-1.004)	0.093
Diabetes (absent/present)	2.434 (1.103-5.370)	0.028
BMI (kg/m ²)	0.884 (0.782-1.000)	0.050

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; Ca-based P-binder, calcium-based phosphate binder; CI, confidence interval; CVD, cardiovascular disease; P, phosphate; OR, odds ratio.

tion of 7 years. The study showed no significant differences in blood pressure changes and incidence of hypertension between active treatment and placebo groups²⁷. Moreover, no significant differences in blood pressure or the incidence of hypertension were found in subgroups with low intake of vitamin D or low serum vitamin D levels. Jorde et al.²⁸ also reported a cross-sectional association between serum 25(OH)D and blood pressure. However, lower serum 25(OH)D levels did not predict future hypertension or high blood pressure. In our study, there were no significant differences in systolic blood pressure, pulse pressure, and baPWV between higher and lower serum 25(OH)D groups in both non-dialysis CKD and HD patients (Table 2).

Studies on the association between vitamin D and blood pressure focused on the effect of mineral metabolism on blood pressure²⁶. In hypertensive animal models, calcium supplementation reduced blood pressure²⁸. Although early data indicated that hypertensive patients had lower serum calcium levels²⁹, evidence regarding the blood pressure lowering effect of calcium supplementation is weak³⁰. Intestinal calcium absorption is increased by vitamin D; therefore, vitamin D has an indirect effect on blood pressure. Vitamin D receptors have been found in vascular smooth muscle cells³¹ and the renin producing juxtaglomerular cells³². Vitamin D inhibits upregulation of the renin-angiotensin system, leading to reduced renal vasoconstriction and atherosclerosis^{32,33}. Vitamin D also can regulate

the expression of the natriuretic peptide receptor³⁴. These results have suggested a direct role of vitamin D on blood pressure, independent of calcium metabolism. In our study, blood pressure was not different according to the 25(OH)D levels in non-dialysis CKD and HD patients. The explanation for our findings is not clear. However, the difference in 25(OH)D levels may have been too small to result in a significant difference in cardiovascular profiles because the majority of subjects had low levels of vitamin D.

Various causes and risk factors for vitamin D deficiency and insufficiency have been reported in HD patients³⁵⁻³⁹. Similar to the general population, age, female sex, low physical activity³⁵, diabetes³⁶, and body adiposity³⁷ are associated with vitamin D deficiency in HD patients. In accordance with eGFR decreases and serum phosphate increases in CKD patients, the hyperphosphaturic hormone FGF-23 released from osteocytes has a role in suppression of renal 1-hydroxylase expression and induction of the degradation of 1,25-(OH)₂D³⁸. Defective photoproduction of cholecalciferol in HD patients was also suggested³⁹. In our data, female sex and presence of diabetes were the only significant factors associated with lower 25(OH)D levels in HD patients after adjusting for covariates (Table 3).

This study has several limitations. First, because of the cross-sectional design, we cannot show a causal relationship between vitamin D and blood pressure. Second, the small number of subjects could have limited statistical sig-

nificance, leading to type II errors. Third, because this study did not perform an intervention using vitamin D, our results cannot infer a protective effect of vitamin D supplementation on blood pressure in CKD patients. A randomized controlled study regarding the effect of vitamin D supplementation on cardiovascular risk is worth investigating. Finally, this study included only Korean non-dialysis CKD and HD patients from a single center. Our results might not be generalizable to other populations and one should be cautious when interpreting this study.

In conclusion, our study demonstrated that vitamin D deficiency was common in both non-dialysis CKD patients and HD patients. Serum 25(OH)D concentration was not a significant factor associated with blood pressure and arterial stiffness among non-dialysis CKD and HD patients. A future, larger-scaled study is needed to clarify this issue.

Declarations

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Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest in this work

Consent for publication

All the co-authors gave their consent for publication

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of CHA Bundang Medical Center. Written consent was acquired from all participants.

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