25-Hydroxyvitamin D Is Associated with Kidney Function: The Dong-gu Study

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Summary Although the kidneys play a leading part in the biosynthesis of vitamin D, there is no consensus regarding the relationship of the vitamin D concentration with kidney function. Thus, we aimed to estimate the correlation among 25-hydroxyvitamin D (25(OH)D), estimated glomerular filtration rate (eGFR), and albumin/creatinine ratio (ACR) in participants aged ≥ 50 y in Korea. This study consisted of 9,166 people who participated in a basic survey of the Dong-gu Study. Following an overnight fast, the blood and urine sample were assessed. The serum 25(OH)D, eGFR, ACR of each subject were measured. When adjusting for covariates and log-transformed ACR (Model III), the lower eGFR value was significantly associated with increasing 25(OH)D levels (<10.0 : 71.5 [70.5–72.4]; 10.0–14.9: 70.0 [69.5–70.4]; 15.0–19.9: 68.7 [68.3–69.2]; ≥ 20.0 : 67.4 [66.8–67.9] mL/min/1.73 m², $p < 0.001$). When adjusted for the same covariates and log-transformed eGFR (Model III), the lower ACR value was significantly associated with increasing 25(OH)D levels (<10.0 : 57.4 [48.0–66.9]; 10.0–14.9: 40.8 [36.5–45.2]; 15.0–19.9: 34.0 [29.5–38.5]; ≥ 20.0 : 34.3 [28.8–39.8] $\mu\text{g}/\text{mg}$ creatinine, $p < 0.001$). In conclusion, the mean values of eGFR were significantly decreased with increasing 25(OH)D levels independent of ACR. In addition, the mean values of ACR were significantly decreased with increasing 25(OH)D levels independent of eGFR in participants aged ≥ 50 y in Korea.

Key Words glomerular filtration rate, albuminuria, 25-hydroxyvitamin D, kidney function

Chronic kidney disease (CKD), which encompasses all degrees of impaired renal function, affects approximately 17% of the U.S. general population (1). A decreased glomerular filtration rate (GFR) is a major cause of cardiovascular disease (CVD) (2) and reduced renal function is associated with the increase of all-cause mortality and CVD events in high-risk patients (3), as well as in the general population (4). Albuminuria is known to a predictor of the mortality and morbidity of CVD, end-stage kidney disease, and CKD progression (5, 6). Thus, the detection and treatment of risk factors associated with decreased GFR and albuminuria may prevent CKD progression and reduce the risk of CVD (7).

Vitamin D plays a vital part in maintaining serum

calcium level (8). Not less than 80% of vitamin D is synthesized from cholesterol by ultraviolet radiation in the skin, while the remaining 10–20% is obtained from diet; fish oil, dairy foods and various supplements (9). First, ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) are ingested through the diet or ultraviolet radiation. These two vitamin D metabolites are hydroxylated within the liver to calcifediol (25(OH)D) and after that, it is hydroxylated within the kidneys to the biologically active metabolite, calcitriol (1,25(OH)₂D) (10). Thus, the kidney has a critical role in the biosynthesis of 1,25(OH)₂D even though there is no concordance regarding the relationship of the vitamin D concentrations with kidney function. Some studies demonstrated positive relationships between the 25(OH)D and the estimated GFR (eGFR) (11, 12); others reported inverse associations (13, 14); still others presented no associa-

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tion (15, 16). These discrepancies may be due to differences in race, age, latitude and CKD status of the subjects.

South Korea has recently become known as a country of vitamin D deficiency (17, 18). However, because there have been only a few vitamin D related studies within the Korean population, whether the low vitamin D levels are correlated with eGFR and albumin/creatinine ratio (ACR) in Korean population needs to be verified. Therefore, we aimed to evaluate the correlation among 25(OH)D, eGFR, and ACR in a population aged ≥ 50 y in Korea.

MATERIALS AND METHODS

Subjects. We conducted this study as a basic survey of the Dong-gu Study. A previous publication has shown the detailed information (19). By using National resident registration data in the Gwangju Metropolitan area from 2007 to 2010, we selected 34,040 potential subjects who were over 50 y old and lived in the district of Dong-gu. We contacted the eligible residents by telephone or e-mail and encouraged them to visit the Dong-gu health center to participate this survey; ultimately, 9,260 subjects were signed up in the Dong-gu Study from 2007 to 2010 and the response rate was 27.2%. After excluding 94 participants who were lacking vital data ($n=91$), such as 25(OH)D or serum creatinine levels, and/or had a high urine ACR $\geq 3,000$ mg/g ($n=3$), which is indicative of nephrotic-range albuminuria or altered vitamin D metabolism (20), we analyzed a total of 9,166 subjects (men: 3,668 and women: 5,498) in this study.

Data collection. The trained staff interviewed the subjects using a questionnaire that included items on smoking, alcohol intake, physical activity, history of diabetes and hypertension medication, and multi-vitamin intake. The smoking status was assessed by self-report; if the participant had smoked more than 100 cigarettes in his whole life, he was counted as a smoker. Alcohol intake was assessed as positive if the participant drank alcohol in last month and physical activity was counted if a subject worked out regularly.

The trained researchers measured the weight, height, and waist circumference of the subjects in units of 0.1 kg or 0.1 cm while the participant was wearing light clothes and socks. The waist circumference was measured at expiration by placing a flexible tape parallel to the floor at the midpoint between the iliac crest and the lowest rib.

Following an overnight fast, the venous blood sample was taken from an antecubital vein of the participant. After the separation of serum on site, the serum was frozen at -70°C until further measure. By using enzymatic methods, the concentrations of serum lipid profile such as high-density lipoprotein cholesterol (HDL-C), triglyceride, total cholesterol (TC) were measured with a Hitachi-7600 automatic biological analyzer (Hitachi Ltd., Tokyo, Japan).

Kidney function. GFR was estimated by the equation of the Chronic Kidney Disease Epidemiology Collabora-

tion (CKD-EPI) (21);

$$\text{eGFR}_{\text{CKD-EPI}} = 141 \times \min\left(\frac{\text{Scr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\text{Scr}}{\kappa}, 1\right)^{-1.209} \\ \times 0.993^{\text{age}} \times 1.018 \text{ (if female)}$$

Urine creatinine was measured using the Jaffé reaction (22) and urine albumin was measured via turbidimetric immunoassay with a Hitachi-7600 automatic biological analyzer (Hitachi Ltd.). ACR was calculated as the concentration of urine albumin (μg) divided by the concentration of urine creatinine (mg) and albuminuria was defined according to the ACR level.

Measurement of serum concentrations of parathyroid hormone (PTH) and 25(OH)D. Serum PTH and 25(OH)D levels were measured with the aid of a microparticle immunoassay system that detected chemiluminescence (ARCHITECT i2000; Abbott Diagnostics, Abbott Park, IL). In a comparative study of automated immunoassays and liquid chromatography-tandem mass spectrometry methods (LC-MS/MS) (23), the Abbott 25(OH)D assay was comparable to LC-MS/MS; the concordance correlation coefficient was 0.85, and the mean bias was 4.56 ng/mL. The coefficient of variation for the total analytic precision of the PTH assay was 9% and the lower detection limit was 1.0 pg/mL. The coefficient of variation for the 25(OH)D assay was 10%, and the lower detection limit was 3.0 ng/mL.

Statistical analysis. We used IBM SPSS software 22.0 (IBM Corp., Armonk, NY) for the statistical analyses. Baseline demographics are presented as number and percent or mean and standard deviation (SD) across levels of 25(OH)D. eGFR and ACR values were transformed to logarithmic values because eGFR and ACR did not show a normal distribution. The mean values of eGFR and ACR according to the 25(OH)D levels were compared by using analysis of covariance (ANCOVA) models. Sex, age, and the month of blood collection were adjusted in Model I. Health behavior variables, medication of anti-hypertension and anti-diabetes, multi-vitamin intake, lipid profile, parathyroid hormone, and the variables of Model I were adjusted in Model II. The log-transformed ACR or log-transformed eGFR and the variables of Model II were adjusted in Model III. As an additional analysis, we plotted the predicted Z-score of 25(OH)D with fractional polynomials with default settings in Stata version 11.0 (StataCorp, College Station, TX). We used as a cut-off for statistical significance a p -value less than 0.05.

RESULTS

General characteristics across the 25(OH)D levels

Table 1 shows the general characteristics across the 25(OH)D levels. Participants with increasing 25(OH)D levels were highly likely to be male, have a higher intake of alcohol, be more physically active, use less anti-diabetes medication, and have a lower intake of multivitamins and a lower percentage of albuminuria ($p<0.05$). Height and weight tended to increase in participants with higher 25(OH)D levels ($p<0.001$). By contrast, triglyceride, HDL-C, PTH, and ACR tended to decrease in participants with higher 25(OH)D levels ($p<0.001$).

Table 1. General characteristics across the 25(OH)D levels.

Variables	25(OH)D (ng/mL)				Total	p
	<10.0	10.0–14.9	15.0–19.9	≥20.0		
n (%)	725 (7.91)	3,326 (36.29)	2,908 (31.73)	2,207 (24.08)	9,166 (100.0)	
Male (%)	104 (14.3)	779 (23.4)	1,321 (45.43)	1,464 (66.33)	3,668 (40.02)	<0.001
Age (y)	66.6±8.47	65.2±8.33	64.7±8.02	65.1±7.95	65.2±8.17	<0.001
Month of blood collection						<0.001
March	11 (1.5)	52 (1.6)	21 (0.7)	6 (0)	90 (1.0)	
April	236 (32.6)	754 (22.7)	500 (17.2)	267 (12.1)	1,757 (19.17)	
May	291 (40.1)	1,207 (36.29)	902 (31.0)	599 (27.1)	2,999 (32.72)	
June	132 (18.2)	888 (26.7)	924 (31.8)	793 (35.9)	2,737 (29.86)	
July	55 (7.6)	425 (12.8)	561 (19.3)	542 (24.6)	1,583 (17.27)	
Height (cm)	154±7.50	156±7.70	159±8.34	162±8.20	158±8.39	<0.001
Weight (kg)	57.3±8.61	59.7±8.97	62.1±9.45	63.1±9.27	61.1±9.33	<0.001
BMI (kg/m ²)	24.2±3.12	24.5±3.03	24.4±2.92	24.1±2.70	24.4±2.93	<0.001
Waist circumference (cm)	154±7.50	156±7.70	159±8.34	162±8.20	158.3±8.39	<0.001
Smoking (%)	61 (8.4)	265 (7.98)	344 (11.8)	326 (14.8)	996 (10.9)	<0.001
Alcohol intake (%)	188 (26.1)	1,236 (37.25)	1,486 (51.26)	1,307 (59.36)	4,217 (46.14)	<0.001
Physically active ¹ (%)	389 (53.7)	2,014 (60.55)	1,885 (64.82)	1,517 (68.74)	5,805 (63.33)	<0.001
Anti-hypertensive medication (%)	266 (37.4)	1,168 (35.33)	1,069 (36.99)	733 (33.4)	3,236 (35.55)	0.04
Anti-diabetes medication (%)	101 (14.2)	444 (13.4)	384 (13.3)	244 (11.1)	1,173 (12.90)	0.04
Multi-vitamin intake (%)	558 (80.9)	2,535 (78.48)	2,187 (77.55)	1,548 (71.87)	6,828 (76.77)	<0.001
Total cholesterol (mg/dL)	217±44.5	207.8±40.07	196.9±37.76	191.6±37.91	201.2±40.03	<0.001
Triglycerides (mg/dL)	161±154	146.3±97.18	139.4±90.95	136.9±94.13	143.0±100.5	<0.001
HDL cholesterol (mg/dL)	53.7±12.5	52.36±11.91	50.92±11.86	50.48±11.89	51.56±11.98	<0.001
PTH (pg/mL)	53.2±31.7	46.03±24.26	41.33±17.55	38.14±15.21	43.20±21.55	<0.001
eGFR (mL/min/1.73 m ²)	69.0±15.0	69.45±13.95	69.09±13.48	68.35±13.31	69.04±13.74	0.04
CKD (%; eGFR<60 mL/min/1.73 m ²)	174 (24.0)	780 (23.4)	677 (23.3)	555 (25.1)	2,186 (23.84)	0.41
ACR (μg/mg creatinine)	60.1±230	40.85±132.0	33.52±94.04	32.96±91.17	38.15±123.9	<0.001
Albuminuria (%, ACR>30 μg/mg creatinine)	174 (24.0)	704 (21.2)	571 (19.7)	418 (19.0)	1,867 (20.39)	0.01

All values are given as n (%) or mean±standard deviation.

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; HDL, high-density lipoprotein; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACR, albumin creatinine ratio.

¹ Subjects who performed 30 min or more of walking at least 5 d a week.

Table 2. ANCOVA analysis of the mean eGFR and ACR values across the 25(OH)D levels.

Variables	25(OH)D levels	Model 1 Mean (95%CI)	Model 2 Mean (95%CI)	Model 3 Mean (95%CI)
eGFR (mL/min/1.73 m ²)	<10.0	70.5 (69.5–71.4)	71.5 (70.6–72.5)	71.5 (70.5–72.4)
	10.0–14.9	69.6 (69.2–70.1)	70.0 (69.6–70.4)	70.0 (69.5–70.4)
	15.0–19.9	68.7 (68.3–69.2)	68.7 (68.3–69.2)	68.7 (68.3–69.2)
	≥20.0	68.1 (67.5–68.6)	67.4 (66.9–68.0)	67.4 (66.8–67.9)
	p value	<0.001	<0.001	<0.001
ACR (μg/mg creatinine)	<10.0	59.2 (50.0–68.4)	53.9 (44.3–63.5)	57.4 (48.0–66.9)
	10.0–14.9	41.6 (37.2–45.9)	39.2 (34.8–43.7)	40.8 (36.5–45.2)
	15.0–19.9	33.8 (29.3–38.3)	34.5 (29.9–39.1)	34.0 (29.5–38.5)
	≥20.0	31.9 (26.4–37.3)	37.2 (31.6–42.7)	34.3 (28.8–39.8)
	p value	<0.001	0.01	<0.001

Model 1, Adjusted by month of blood collection, sex and age.

Model 2, Adjusted by Model 1 plus waist circumference, smoking, alcohol intake, physical activity, anti-hypertension medications, anti-diabetes medication, multi-vitamin intake, total cholesterol, triglyceride, HDL cholesterol, and PTH.

Model 3, Adjusted by Model 2 plus log-transformed ACR or log-transformed eGFR.

Fig. 1. Distribution of the Z-score of 25(OH)D cross the eGFR levels.

ANCOVA analysis of the mean eGFR and ACR values across the 25(OH)D levels

Table 2 shows ANCOVA analysis of the mean values (95% confidence interval [CI]) of eGFR and ACR across the 25(OH)D levels. When adjusted with covariates (sex, age, month of blood collection, health behavior variables, medication for anti-hypertension and anti-diabetes, multivitamin intake, lipid profile, parathyroid hormone) and log-transformed ACR (Model III), lower eGFR values were significantly associated with increasing 25(OH)D levels (<10.0: 71.5 [70.5–72.4]; 10.0–14.9: 70.0 [69.5–70.4]; 15.0–19.9: 68.7 [68.3–69.2]; ≥ 20.0 : 67.4 [66.8–67.9] mL/min/1.73 m², $p < 0.001$). When adjusted for the same covariates and log-transformed eGFR (Model III), the lower ACR values were significantly associated with increasing 25(OH)D levels (<10.0: 57.4 [48.0–66.9]; 10.0–14.9: 40.8 [36.5–45.2]; 15.0–19.9: 34.0 [29.5–38.5]; ≥ 20.0 : 34.3 [28.8–39.8] $\mu\text{g}/\text{mg}$ creatinine, $p < 0.001$).

Distribution of the Z-score of 25(OH)D across the eGFR levels

Figure 1 shows the distribution of the Z-score of 25(OH)D across the eGFR levels. The Z-score of 25(OH)D was at its highest level at eGFR 45–59 mL/min/1.73 m². In addition, when the eGFR was lower than 45–59 mL/min/1.73 m², the Z score of 25(OH)D was reduced with decreasing levels of eGFR.

DISCUSSION

We estimated the relationship among ACR, eGFR, and 25(OH)D with subjects aged ≥ 50 y in Korea. Our results demonstrated that the lower eGFR and ACR values were significantly associated with higher 25(OH)D levels in subjects aged ≥ 50 y in Korea.

In our study, when adjusted for covariates, the lower eGFR values were significantly associated with increasing levels of 25(OH)D. Previous researchers have inves-

tigated the relationship of 25(OH)D with eGFR, but results have been inconsistent (11–16). The exact reasons for these discrepancies are unknown, but there are some explanations. First, the prevalence of severe renal impairments might affect the relationship; studies of CKD patients identified a positive association between the eGFR and vitamin D levels (12, 24), while those without CKD patients found a negative association (14, 25). Second, the association between eGFR and vitamin D varied according to the eGFR and 25(OH)D concentrations of the participants (11, 26). Recently, a negative association between eGFR and 25(OH)D has been reported in a Korean people known as a vitamin D deficient population. In the survey with 11,336 Korean subjects, 25(OH)D was negatively correlated with eGFR (13). Furthermore, in the cross-sectional study with 1,648 Korean adults, the elevated eGFR concentrations were highly correlated with reduced 25(OH)D level (14).

It was unexpected that 25(OH)D was inversely correlated with eGFR; previous studies have indicated that 25(OH)D has renoprotective effects (27). However, various mechanisms may underlie this negative association between the eGFR and the 25(OH)D. Because the hydroxylation of 25(OH)D to the biologically active metabolite occurs within the kidneys, renal deficiency results in reduced 1,25(OH)₂D concentrations due to the stagnating metabolism of 25(OH)D (28). In addition, impaired metabolism may be mediated by the activity of fibroblast growth factor 23, which suppresses the hydroxylation of 25(OH)D and encourages the catabolism of 1,25(OH)₂D (29). Thus, it is plausible that 25(OH)D concentrations are higher in the initial stages of CKD than in the normal eGFR (28). A previous study with KNHANES 2011–2012 (13) reported that the highest 25(OH)D values occurred at the level of eGFR 61–90 mL/min/1.73 m². However, our result showed that the mean 25(OH)D value was at its highest

level at eGFR 45–59 mL/min/1.73 m². The gap in the eGFR level at which 25(OH)D was highest may be due to the difference in the population age (previous study: 51.2±16.2 y; our study: 65.2±8.2 y) and eGFR measurement (previous study: MDRD equation; our study: CKD-EPI equation).

In our study, after being adjusted for covariates, the reduced ACR value was significantly correlated with the elevated quartile of 25(OH)D. A cross-sectional study with 15,068 in the United States demonstrated that the decreased 25(OH)D levels were highly related to the prevalence of albuminuria (30). In a previous KNHANES 2012 study with 4,948 subjects (31), vitamin D deficiency was significantly associated with an elevated ACR level, similar to our result. The correlation between albuminuria and 25(OH)D levels is well established (32). First, the renin-angiotensin system (33) and nuclear factor- κ B (NF- κ B) pathway might be inhibited by vitamin D (34). Second, vitamin D directly affects cell proliferation, differentiation, and apoptosis (35, 36). Moreover, the relation of vitamin D with kidney function seems to be bidirectional because it appears that renal dysfunction might lead to decreases in vitamin D levels. Vitamin D is reabsorbed in the proximal tubule via the actions of megalin and cubilin (37); thus, it is also possible that the increased filtration of albumin into the urinary space interferes with vitamin D reabsorption, which, in turn, leads to greater losses of vitamin D via the urine.

A relatively large sample size and the population-based design are strengths of our study. However, there are certain limitations. First, because of the cross-sectional design, we were unable to examine the causal relationships among 25(OH)D, eGFR and ACR. Second, because our study participants had very low levels of vitamin D, the outcomes could be affected by a skewed distribution of vitamin D. However, KNHANES data, which is representative of Koreans (38), showed similar low levels of vitamin D. In the study with KNHANES data, 38% subjects exhibited less than 15.0 ng/mL (31) and 75% subjects less than 20.5 ng/mL (13). Third, information on sunlight exposure and dietary vitamin D intake was not examined. But instead, we have investigated “multi-vitamin intake” and “physical activity”, which presumably reflect sunlight exposure and dietary vitamin D intake. Finally, we estimated GFR using the equation for CKD-EPI for improving the imprecision and bias. However, because the CKD-EPI equation was developed based on serum creatinine, it is influenced by muscle mass, dietary food, and secretion in renal tubules (39).

In conclusion, the mean values of eGFR were significantly decreased with increasing 25(OH)D levels independent of ACR. Moreover, the mean values of ACR were significantly decreased with increasing 25(OH)D levels independent of eGFR in participants aged ≥ 50 y in Korea.

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