INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Risk Factors for Vitamin D Deficiency in Patients with Chronic Kidney Disease

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Abstract

Objective We conducted a cohort study to identify the risk factors for vitamin D deficiency in predialyzed patients with chronic kidney disease (CKD).

Methods An observational study of 135 outpatients with stage 3-5 CKD was undertaken. Clinical and biochemical parameters were analyzed in terms of nutritional status, inflammation, and mineral metabolism in relation to serum levels of 25-hydroxyvitamin D [25(OH)D]. Levels of 25(OH)D lower than 15 ng/mL were considered to be deficient.

Results The 25(OH)D-deficient group had a higher body mass index (24.1±4.2 kg/m^2 vs. 22.5±4.0 kg/m^2, p=0.0322), and had more diabetic patients (27.9% vs. 3.6%, p=0.0003). The multivariate analysis revealed that body mass index (odds ratio=2.758; 95% CI, 1.048-7.721; p=0.0398), the presence of diabetes (odds ratio=7.792; 95% CI, 1.808-55.439; p=0.0043), lower hemoglobin concentration (odds ratio=0.297; 95% CI, 0.099-8.732; p=0.821), higher serum levels of non-HDL cholesterol (odds ratio=3.570; 95% CI, 1.449-9.442; p=0.0053) and triglyceride (odds ratio=2.447; 95% CI, 0.779-1.776; p=0.0258) were the factors associated with low 25(OH)D levels.

Conclusion Vitamin D deficiency was common among the predialysis CKD patients, and the factors identified as being associated with vitamin D deficiency were diabetes and obesity.

Key words: chronic kidney disease, vitamin D deficiency, obesity, diabetes

(Intern Med 51: 845-850, 2012)
(DOI: 10.2169/internalmedicine.51.6897)

Introduction

Low 25-hydroxyvitamin D [25(OH)D] levels are common in patients with chronic kidney disease (CKD), and the prevalence of this condition increases as kidney function declines (1, 2). Several factors, including increasing age and comorbid conditions, such as diabetes and hypertension, have consistently been associated with low 25(OH)D levels in individuals with both dialysis-dependent and nondialysis-dependent CKD (3, 4). Analysis of the data obtained in the Third National Health and Nutrition Examination Survey (NHANES) conducted in the United States showed an inverse association between the body mass index (BMI) and 25(OH)D levels of persons with CKD (5), but a longitudinal study found no such association (6).

Evidence linking low 25(OH)D levels and cardiovascular risk factors in nondialysis-dependent CKD patients has been accumulating in recent years (7). The NHANES analyses reported a positive association between low 25(OH)D levels and the mortality of persons with CKD defined as either an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or the presence of microalbuminuria (5). Similarly, a single-center study by Ravani et al. reported independent associations between low 25(OH)D levels and all-cause mortality (6). However, another community-based study did not find any association between 25(OH)D levels and cardiovascular mortality in community-dwelling adults (8). In the present study, we attempted to identify factors associated with low 25(OH)D levels in patients with stages 3 to 5 CKD who had been followed up in our outpatient clinic.

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Received for publication November 7, 2011; Accepted for publication December 26, 2011
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Materials and Methods

Study population

This was a cross-sectional cohort study. We analyzed data in our electronic health record-based CKD registry. The development and validation of an electronic health record-based CKD registry at the Kidney Center of Tokyo Women's Medical University has been described in detail elsewhere (9). Patients who met the following inclusion criteria as of September 1, 2006, were included in the CKD registry: patients who had 2 estimated glomerular filtration rate (eGFR) values <60 mL/min/1.73 m^2 using the modification of diet in renal disease (MDRD) study equation for Japanese people (10). Patients under 20 years of age and patients already diagnosed with end-stage renal disease (ESRD) that required renal replacement therapy were excluded, and patients who had an active infection, severe cardiovascular disease, or ascites with liver disease were also excluded. Patients who met the inclusion/exclusion criteria were included in the analysis. The underlying renal diseases of the patients who were included in the study were diabetic nephropathy (n=24) and nephropathy of non-diabetic origin (n=111). The Institutional Research Ethics Committee approved the study protocol, and all patients signed an informed consent form. This study was conducted in compliance with the Declaration of Helsinki.

The CKD registry contains patients' demographic information, prescribed medications, laboratory data, and information about their treatment. Blood pressure was measured with a brachial sphygmomanometer three times after the subject had rested in the supine position for at least 10 minutes, and the average value of the three measurements was adopted. Body mass index (BMI) was calculated by dividing body weight (kg) by body height $(m)^2$. Prescribed doses of oral vitamin D analogue (alfacalcidol) were recorded. Alfacalcidol was administered when serum calcium was less than 8.5 mg/dL and serum intact parathyroid hormone (PTH) higher than 150 pg/mL after titration with CaCO3.

Laboratory parameters

Fasting blood specimens were collected to measure blood chemistry parameters. Serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium, phosphorus, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, alkaline phosphatase, glucose, and C-reactive protein (CRP), and hemoglobin concentrations were measured by routine laboratory methods. Low-density lipoprotein (LDL) cholesterol values were calculated by using the Friedewald formula. The non-HDL cholesterol value was calculated by subtracting the HDL cholesterol value from the total cholesterol value. Serum intact parathyroid hormone (PTH) was measured once. Serum 25(OH)D was measured by radioimmunoassay (DiaSorin Inc., Stillwater, MN, USA) at a commercial clinical laboratory (SRL, Tokyo, Japan). Five blinded quality-control samples were included in the batch analysis; the coefficient of variation for 25(OH)D was 33.3%. The coefficients of intra- and inter-day variation of routine quality-control data for 25(OH)D reported by SRL ranged between 4.3% and 7.0% (mean levels of 8.5, 14.1, and 50.9 ng/mL).

Statistical analysis

The variables with a normal distribution were expressed as means ± SD, and those that did not have a normal distribution were expressed as medians and 25-75 percentiles. Categorical variables were expressed as numbers and percentages. Comparisons between continuous variables were performed by using the Mann-Whitney U test. The Kruskal-Wallis test was used for comparisons of more than two groups. Categorical variables were compared using the chi square test. Spearman's bivariate correlation was used to assess the strength of the associations between the analyzed data and the 25(OH)D levels. Statistically significant variables were selected as potential independent predictors of 25 (OH)D deficiency in the multivariate binary logistic regression analysis, with the dependent variable being the presence or absence of 25(OH)D deficiency. All of the statistical data analyses were conducted with the JMP, version 9.1 software program (SAS Institute Japan, Tokyo, Japan). The protocol of this study was approved by the Institutional Review Board of Tokyo Women's Medical University.

Results

Patient characteristics

The distribution of the 135 patients according to CKD stage was: stage 3, 68 patients (50.4%); stage 4, 48 patients (35.6%); and stage 5, 19 patients (14.0%). The clinical and biochemical data of the 135 patients are shown in Table 1. As shown in Fig. 1, the serum 25(OH)D levels of the patients with stage 3, 4, and 5 CKD expressed as the median value and interquartile range were: stage 3, 13.6 ng/mL (9.5-21.8); stage 4, 12.9 ng/mL (7.7-18.3); and stage 5, 13.0 ng/mL (9.5-20.2). The serum 25(OH)D levels tended to decrease with the stage of the CKD, but the differences in values between the stages did not reach the levels of statistical significance (p=0.6789). No patient had abnormal liver function.

Table 2 compares the data analyzed in relation to serum 25(OH)D levels above and below the cut-off point of 15 ng/mL. The 25(OH)D-deficient group had a higher BMI (24.1±4.2 kg/m^2 vs. 22.5±4.0 kg/m^2, p=0.0322), and had more diabetic patients (27.9% vs. 3.6%, p=0.0003). There was no significant difference in fasting blood glucose levels between the two groups (98.8±23.8 mg/dL vs. 96.2±26.7 mg/dL). Lower hemoglobin concentrations and higher serum levels of non-HDL cholesterol and triglyceride were detected in the 25(OH)D-deficient group. There were no differences between the groups in renal function, assessed on the basis of

Table 1. Clinical and Biochemical Characteristics of Study Population

Variable	n=135
Age (years)	60.5 ± 12.7
Men (%)	72 (53%)
Body mass index (kg/m^2)	23.4 ± 4.2
Diabetes	24 (18%)
Systolic blood pressure (mmHg)	124.3 ± 12.3
Diastolic blood pressure (mmHg)	73.3 ± 9.4
Pulse pressure (mmHg)	51.0 ± 10.7
Calcium (mg/dL)	9.0 ± 0.5
25(OH)D (ng/mL)	13.0(8.7-19.9)
Phosphorus (mg/dL)	3.5 ± 0.8
Alkaline phosphatase (U/L)	217.9 ± 80.6
Intact-PTH (pg/mL)	102 (72-142)
Albumin (g/dL)	4.0 ± 0.4
C-reactive protein (mg/L)	0.7 (0.5-1.4)
Creatinine (mg/dL)	2.0 ± 0.9
eGFR (mL/min/1.73m^2)	29.6 ± 11.6
Proteinuria (g/gCr)	0.57 (0.18-1.36)
Hemoglobin (g/dL)	12.3 ± 1.9
Total cholesterol (mg/dL)	196.2 ± 48.0
HDL-cholesterol (mg/dL)	52.6 ± 17.2
Non-HDL-cholesterol (mg/dL)	142.2 ± 43.8
LDL-cholesterol (mg/dL)	110.5 ± 3.0
Triglyceride (mg/dL)	157.9 ± 89.3
Aspartate aminotransferase (IU/L)	18.1 ± 4.3
Alanine aminotransferase (IU/L)	17.0 ± 5.7
Glucose (mg/dL)	97.7 ± 25.0
Treatment with ACEI or ARB	100 (74%)
Treatment with statin	52 (39%)
Treatment with ESA	24 (18%)
Treatment with Vitamin D	33 (24%)

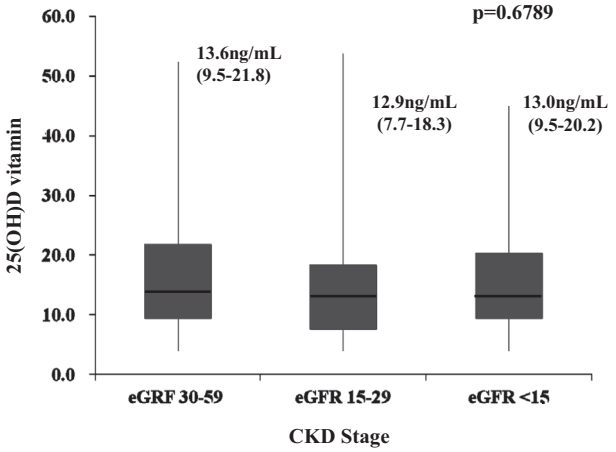

Figure 1. Serum 25(OH)D levels of the subjects with stage 3-5 chronic kidney disease (CKD).

the serum creatinine and eGFR values. Proteinuria (g/g creatinine) in spot urine samples tended to be higher in the 25 (OH)D-deficient group, but the difference did not reach the levels of statistical significance (p=0.0520). The results for mineral metabolism showed no significant differences between the two groups in the serum levels of calcium, phosphorus, alkaline phosphatase, and intact PTH or the prevalence of vitamin D therapy or dose of alfacalcidol (0.7±1.2 μg/week vs. 0.5±0.9 μg/week, p=0.3148). The results for the nutritional parameters, i.e., serum albumin levels (4.0±0.4 g/dL vs. 4.1±0.4 g/dL, p=0.0542) showed no significant difference between the two groups in serum 25(OH)D levels. The inflammatory state according to the CRP levels showed no significant difference between the two groups in serum 25(OH)D levels (4.0±0.4 mg/L vs. 4.1±0.4 mg/L, p=0.0542).

Factors associated with low 25(OH)D levels

The results of the univariate analysis (Table 3) showed that the serum 25(OH)D levels were inversely correlated with BMI (r=-0.218, p=0.0114) and the serum triglyceride levels (r=-0.182, p=0.0354), and that the serum 25(OH)D levels were positively correlated with age (r=0.286, p=0.0310), serum calcium levels (r=0.221, p=0.0118), and hemoglobin concentrations (r=0.184, p=0.0333). There was no significant association between the serum 25(OH)D levels and alfacalcidol dose (r=-0.121, p=0.1660).

A logistic regression model was used to evaluate independent factors associated with low 25(OH)D levels. The multivariate analysis (Table 4) revealed that BMI (odds ratio=2.758; 95% CI, 1.048-7.721; p=0.0398), the presence of diabetes (odds ratio=7.792; 95% CI, 1.808-55.439; p=0.0043), lower hemoglobin concentrations (odds ratio=0.297; 95% CI, 0.099-0.821; p=0.0188), higher serum levels of non-HDL cholesterol (odds ratio=3.570; 95% CI, 1.449-9.442; p=0.0053) and triglyceride (odds ratio=2.447; 95% CI, 1.028-5.997; p=0.0431) were the independent factors associated with low 25(OH)D levels.

Discussion

The risk factors for vitamin D deficiency in CKD patients have never been clearly identified. The results of this study showed a high prevalence of vitamin D deficiency in non-dialyzed CKD patients, and we demonstrated that diabetes and obesity were the factors most closely associated with this condition.

In CKD patients, 25(OH)D deficiency is associated with age, the same as it is in the general population (11). This finding could be explained by a combination of factors, including poor nutrition, gastrointestinal disorders, or a lack of vitamin D synthesis because of little exposure to sun light. Dietary restriction and loss of appetite due to uremia may be strong determinants of 25(OH)D deficiency in CKD patients (2). The nutritional parameters analyzed in this study did not differ according to patients' 25(OH)D levels, so they may not be considered as a global malnutrition marker.

BMI was higher in the patient group with low 25(OH)D levels in this study, and obesity was associated with low 25 (OH)D. Several studies in the general population have shown a high prevalence of vitamin D deficiency in obese subjects (12, 13), and an increase in the serum 25(OH)D levels of obese patients has been observed after weight reduction (14). In CKD, the vitamin D deficiency in the spec-

Table 2. Comparison of Clinical and Biochemical Data Regarding 25(OH)D Levels

Clinical and analytical data	25(OH)D ≥ 15ng/mL n=56 (41%)	25(OH)D < 15ng/mL n=79 (59%)	p value
Age (years)	62.1 ± 12.3	59.4 ± 13.0	0.2261
Men (%)	30/56 (53.6)	42/79 (53.2)	0.9628
Body mass index (kg/m^2)	22.5 ± 4.0	24.1 ± 4.2	0.0322
Diabetes	2/56 (3.6)	22/79 (27.9)	0.0003
Systolic blood pressure (mmHg)	124.1 ± 12.3	124.4 ± 12.4	0.8824
Diastolic blood pressure (mmHg)	73.4 ± 8.3	73.2 ± 10.1	0.8577
Pulse pressure (mmHg)	50.7 ± 11.6	51.1 ± 10.1	0.8394
Calcium (mg/dL)	9.1 ± 0.5	8.9 ± 0.5	0.0537
Phosphorus (mg/dL)	3.6 ± 1.0	3.3 ± 0.6	0.0729
Alkaline phosphatase (U/L)	219.9 ± 67.4	216.4 ± 89.2	0.8095
Intact-PTH (pg/mL)	87 (67-128)	105 (74-154)	0.0701
Albumin (g/dL)	4.1 ± 0.4	4.0 ± 0.4	0.0542
CRP (mg/L)	0.7 (0.5-1.2)	0.8 (0.5-1.6)	0.2195
Creatinine (mg/dL)	1.9 ± 0.9	2.1 ± 1.0	0.3929
eGFR (mL/min/1.73m^2)	30.5 ± 10.9	28.9 ± 12.1	0.4161
Proteinuria (g/gCr)	0.45 (0.11-0.96)	0.68 (0.20-2.13)	0.0520
Hemoglobin (g/dL)	12.7 ± 1.7	12.0 ± 2.0	0.0324
Total cholesterol (mg/dL)	189.0 ± 47.1	201.3 ± 48.3	0.1420
HDL-cholesterol (mg/dL)	53.4 ± 16.1	52.1 ± 18.0	0.6482
Non-HDL-cholesterol (mg/dL)	133.3 ± 41.3	148.5 ± 44.8	0.0465
LDL-cholesterol (mg/dL)	104.8 ± 33.9	114.6 ± 42.1	0.1505
Triglyceride (mg/dL)	138.6 ± 74.6	171.5 ± 96.5	0.0345
Aspartate aminotransferase (IU/L)	18.6 ± 4.4	17.8 ± 4.2	0.2851
Alanine aminotransferase (IU/L)	17.4 ± 5.0	16.8 ± 6.2	0.5470
Glucose (mg/dL)	96.2 ± 26.7	98.8 ± 23.8	0.5618
Treatment with ACEI or ARB	41/56	59/79	0.8478
Treatment with statin	19/56	33/79	0.3562
Treatment with ESA	6/56	18/79	0.0707
Treatment with Vitamin D	13/56	20/79	0.7795

trum of obesity has not been fully explored, and the cause of the relationship between obesity and vitamin D deficiency is not well known. Although this finding may be attributable to the low exposure of obese individuals to sunlight, one of the most widely accepted ideas is that because vitamin D is a fat-soluble substance, it can easily be sequestered and stored in adipose tissue and then slowly released as needed (15).

Diabetes was independently associated with vitamin D deficiency in our patients. There is increasing evidence that vitamin D is involved in the pathophysiology of insulin resistance, diabetes, and metabolic syndrome (16, 17). There are several lines of evidence supporting a role of vitamin D in pancreatic β-cell function (18). It seems that vitamin D stimulates pancreatic insulin secretion by increasing the ability of β-cells to synthesize insulin and accelerating the conversion of proinsulin to insulin (16). Vitamin D directly stimulates insulin receptor expression, thereby increasing the insulin response to glucose stimulation, and it indirectly stimulates insulin receptor expression by regulating the intracellular calcium concentration. Thus, it seems that both insulin resistance and type 2 diabetes are mediated by involving the mechanisms of 25(OH)D deficiency (18).

25(OH)D deficiency is associated with higher mortality in CKD and non-CKD populations, and various mechanistic links have been proposed to explain the associations (19-21), including suppression of the renin-angiotensin-aldosterone system, cardiac myocyte hypertrophy, and vascular calcification. Analyses of NHANES III study that included data obtained from patients with a low eGFR and albuminuria, of which 70% of their study participants had stage 1 and 2 CKD, showed a similar increase in risk of all-cause mortality associated with 25(OH)D levels < 15 ng/mL (5). A single-center study reported higher risks of progression of kidney disease and death in stage 2-5 CKD patients who had low 25(OH)D levels (6). However, a recent study reported a lack of association between 25(OH)D level and cardiovascular mortality (8). A prospective study is needed to determine the role of vitamin D deficiency in CKD progression and mortality in CKD patients.

The present study had several limitations. The sample size was small, and despite careful adjustments in our statistical analyses, it was impossible to rule out the presence of residual confounding factors in relation to vitamin D deficiency. Second, there was attrition bias, because we included only patients whose serum 25(OH)D level had been measured. We therefore adjusted for several potential confounding variables in this analysis. Third, we cannot rule out an effect of

Table 3. Spearman Bivariate Correlation between 25(OH)D Levels and Variables Studied

Variable	Rho	p value
Age (years)	0.186	0.0310
Body mass index (kg/m^2)	-0.218	0.0114
Systolic blood pressure (mmHg)	-0.041	0.6373
Diastolic blood pressure (mmHg)	-0.027	0.7582
Pulse pressure (mmHg)	-0.044	0.6140
Calcium (mg/dL)	0.221	0.0118
Phosphorus (mg/dL)	0.104	0.2301
Alkaline phosphatase (U/L)	0.004	0.9660
Intact-PTH (pg/mL)	-0.148	0.0875
Albumin (g/dL)	0.094	0.2779
C-reactive protein (mg/L)	0.019	0.8221
Creatinine (mg/dL)	-0.063	0.4686
eGFR (mL/min/1.73m^2)	0.072	0.4024
Proteinuria (g/gCr)	-0.165	0.0566
Hemoglobin (g/dL)	0.184	0.0333
Total cholesterol (mg/dL)	-0.106	0.2195
HDL-cholesterol (mg/dL)	0.043	0.6218
Non-HDL-cholesterol (mg/dL)	-0.122	0.1582
LDL-cholesterol (mg/dL)	-0.071	0.4124
Triglyceride (mg/dL)	-0.182	0.0354
Aspartate aminotransferase (IU/L)	0.094	0.2779
Alanine aminotransferase (IU/L)	0.094	0.2745
Glucose (mg/dL)	-0.127	0.1423
Alfacalcidol (μg/week)	-0.121	0.1660

Table 4. Logistic Regression Multivariate Analysis: Potential Predictors of Vitamin 25(OH)D Deficiency

Independent variables	Odds ratio	95%CI	p value
Age >60 years	0.497	0.195 - 1.221	0.1280
Sex (men)	1.472	0.562 - 3.965	0.4326
Body mass index >25kg/m^2	2.758	1.048 - 7.721	0.0398
Diabetes	7.792	1.808- 55.439	0.0043
Calcium >8.9mg/dL	0.532	0.209 - 1.315	0.1718
Phosphorus >3.4mg/dL	0.502	0.204 - 1.190	0.1184
Intact-PTH >102pg/mL	0.862	0.331 - 2.203	0.7562
Albumin > 4g/dL	0.608	0.249 - 1.453	0.2633
Proteinuria >0.57g/gCr	0.779	0.308 - 1.923	0.5895
Hemoglobin >12.4g/dL	0.297	0.099 - 0.821	0.0188
Non-HDL-Cholesterol >134mg/dL	3.570	1.449 - 9.442	0.0053
Triglyceride >137mg/dL	2.447	1.028 - 5.997	0.0431
Alfacalcidol 1μg/week	1.164	0.779 - 1.776	0.4618

Model adjusted r^2=0.243. Dependent variable: 25(OH)D deficiency <15 ng/m

treatment with vitamin D analogues on the serum 25(OH)D levels (22). Even though we showed a common policy for starting vitamin D analogue for CKD patients, we did not rule out the effect of the timing of vitamin D supplementation.

In conclusion, the prevalence of vitamin D deficiency was higher among the nondialyzed CKD patients, and the factors associated with this condition were diabetes and obesity. Given the possible benefits of maintaining adequate vitamin D status in CKD, well designed interventional trials that take into account subgroups at high risk for vitamin D deficiency are needed to develop effective strategies for the prevention and treatment of vitamin D deficiency.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

This study was supported by a Grant-in-Aid from the Japan Promotion Society for Cardiovascular Diseases.

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