Original Article

Vitamin D Deficiency in Patients with Stages 1 and 2 Chronic Kidney Disease in Southern China

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Abstract

Aim: We aim to investigate the incidence and associated factors of vitamin D deficiency, a seldom reported factor, in patients with stages 1 and 2 chronic kidney disease (CKD) in southern China. **Methods:** We conducted a single-center observational study. Hospitalized patients over 14 years old, who were diagnosed with stages 1 and 2 CKD and had their serum 25-hydroxyvitamin D [25 (OH) D] measured, were included. Patients were divided into vitamin D deficient and non-deficient groups depending on the cutoff serum 25 (OH) D value of 37 nmol/L. Clinical and biochemical parameters were evaluated for associated factors of vitamin D deficiency by logistic regression. **Results:** A total of 118 patients were included, of which 62 (52.5%) were vitamin D insufficient and 47 (39.8%) were vitamin D deficient. Using multivariate binary logistic regression analysis, high serum level of gamma-glutamyl transpeptidase (GGT) (OR = 5.163; 95%CI, 1.105-24.130; $P = 0.037$), dyslipidemia (OR = 3.083; 95%CI, 1.029-9.243; $P = 0.044$), 24-hour urinary protein excretion (UPE) ≥3.5 g/24 hrs (OR = 5.010; 95%CI, 1.316-19.074; $P = 0.018$), and treatment with glucocorticoids (OR = 2.973; 95%CI, 1.093-8.084; $P = 0.033$) were independently associated with vitamin D deficiency. In addition, among different types of nephropathy, minimal change disease (MCD) had the highest incidence (85.7%) of vitamin D deficiency. **Conclusion:** Poor vitamin D status is common in patients with stages 1 and 2 CKD in southern China. The incidence of vitamin D deficiency is 39.8%. High serum GGT level, dyslipidemia, 24-hour UPE ≥3.5 g/24 hrs, and treatment with glucocorticoids are independent associated factors of vitamin D deficiency.

Keywords: *25-hydroxyvitamin D, chronic kidney disease, vitamin D deficiency*

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Introduction

Mounting evidence shows that chronic kidney disease (CKD) is a major global health problem nowadays. More than 10% of the entire population is in different stages of CKD.[1]

Poor vitamin D status, including vitamin D insufficiency and deficiency, has a high prevalence in patients with CKD, and the prevalence increases as kidney function declines.[2,3] 25-hydroxyvitamin D [25 (OH) D], the major circulating form of vitamin D, is the main storage of vitamin D in the body and is usually measured for evaluating vitamin D status.[4] According to the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, vitamin D insufficiency is defined as a serum concentration of 25 (OH) D between 15 ng/mL and 30 ng/mL (1 ng/mL is equivalent to 2.5 nmol/L), whereas vitamin D deficiency is defined as a serum concentration of 25 (OH) D lower than 15 ng/

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mL.[4] It has been shown that vitamin D deficiency is associated with CKD-mineral and bone diseases and deterioration of renal function.[5] It is also reported that vitamin D deficiency is linked to increased all-cause and cardiovascular mortality in CKD patients.[6]

Most of the research about poor vitamin D status in CKD patients has been focused on stage 3-5 CKD. Monitoring serum 25 (OH) D concentration is only suggested in stage 3-5 CKD patients by KDIGO guidelines at present.[4] However, the status of vitamin D in patients with stages 1 and 2 CKD is seldom reported. Due to the poor outcome of vitamin D deficiency, we postulate that it is necessary to monitor serum 25 (OH) D in patients with stages 1 and 2 CKD. In this study, we aim to investigate the incidence and associated factors of vitamin D deficiency in patients with stages 1 and 2 CKD in southern China.

Methods

Study design and population

This was an observational study, which included hospitalized patients in Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China from January 2014 to May 2017. Patients who met the following criteria were included: a) those who were diagnosed with CKD conforming to the 2013 KDIGO guidelines;[7] b) those with the estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2; and c) those who had their levels of serum 25(OH) D measured. Patients less than 14 years old were excluded. This study was conducted in compliance with the Declaration of Helsinki and was approved by the ethical committee in Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China.

Serum concentration of 25 (OH) D ≥75 nmol/L was defined as normal, 37-75 nmol/L as vitamin D insufficiency, and <37 nmol/L as vitamin D deficiency.[4] Depending on the serum 25 (OH) D level, the patients were divided into vitamin D deficient group and vitamin D non-deficient group with the cutoff value of 37 nmol/L. The patients' in-hospital clinical and laboratory data, diagnosis, treatments, and complications were collected for research. Renal biopsy was performed to make an accurate diagnosis if necessary and written informed consent had been obtained from all patients prior to renal biopsy.

Laboratory assays

Blood hemoglobin concentration, serum 25 (OH) D, bone alkaline phosphatase (BALP), alkaline phosphatase (ALP), calcium, corrected calcium, phosphorus, iron, albumin, creatinine, cystatin C, total cholesterol (CHOL), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), ApoA1 and ApoB, and 24-hour urinary protein excretion (UPE) were measured as previously described.[8] Serum aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl transpeptidase (GGT) were measured with the AU5800 automatic biochemistry analyzer (Beckman Coulter, US).

Other covariates

Blood pressure was measured with a brachial sphygmomanometer three times after the patient had rested in the supine position for at least 10 minutes, and the average value of the three measurements was adopted. eGFR was estimated by the CKD-EPI Cystatin and Creatinine 2012 Equation.[7] Treatments with renin-angiotensin system inhibitors (RASI) and glucocorticoids, along with the complication of infection, were recorded.

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables as means ± standard deviations (SDs) (normally distributed variables) or as medians with interquartile range (skewed distributed variables). Categorical variables were compared by the Chi-square test. Comparisons between continuous variables of the two groups were performed by the Student's *t*-test (normally distributed variables) or the Mann-Whitney U test (skewed distributed variables). Comparisons among continuous variables of more than two groups were performed by the one-way ANOVA (normally distributed variables) or the Kruskal-Wallis test (skewed distributed variables). Statistically significant variables, compared between vitamin D deficient and non-deficient groups, were chosen as potentially independent associated factors of vitamin D deficiency for multivariate binary logistic regression analysis. All statistical tests were two-sided and a *P* value <0.05 was considered statistically significant. All of the statistical analyses were performed with Statistical Product and Service Solutions (SPSS) 19.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

One hundred and eighteen CKD patients with eGFR ≥60 ml/min/1.73 m^2 were included in this study. Fifty-eight (49.2%) patients were in CKD stage 1 while the remaining 60 (50.8%) were in stage 2. Renal biopsies were performed on 72 (61.1%) patients. The composition of primary diseases were as follows: IgA nephropathy (IgAN) (24/118, 20.3%),

Table 1: Comparison of clinical and biochemical characteristics between vitamin D deficient and nondeficient groups in patients with stages 1 and 2 chronic kidney disease

Characteristic	Overall (*n*=118)	Vitamin D deficient (25(OH) D <37nmol/L) (*n*=47)	Vitamin D nondeficient (25(OH) D ≥37nmol/L) (*n*=71)	*P**
Age (years)	43.8±17.3	41.0±18.8	45.7±16.1	0.156
Male sex, *n* (%)	60 (50.8)	29 (61.7)	31 (43.7)	0.055
Diabetes, *n* (%)	18 (15.3)	9 (19.1)	9 (12.7)	0.338
SBP (mmHg)	126.8±18.3	124.6±17.6	128.3±18.8	0.284
DBP (mmHg)	78.8±9.5	78.2±8.2	79.1±10.4	0.596
Hemoglobin (g/L)	129.0±24.1	130.5±28.4	128.0±20.9	0.614
Serum parameters				
25(OH) D (nmol/L)	43.0±20.1	23.4±7.5	55.9±14.6	<0.001□
AST	23.1±12.6	24.9±15.1	22.0±10.6	0.217
ALT	20.4±14.2	22.2±14.9	19.2±13.8	0.269
GGT	20.0 (15.0-44.8)	36.0 (18.0-57.0)	19.0 (14.0-37.0)	0.004□
BALP (μg/L)	11.0 (7.0-15.0)	11.0 (7.0-17.0)	11.0 (7.0-15.0)	0.800
ALP (U/L)	72.9±31.3	78.5±38.3	69.2±25.3	0.150
Corrected calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	0.063
Phosphorus (mmol/L)	1.2±0.2	1.2±0.3	1.2±0.2	0.350
Iron (μmol/L)	13.7±64	12.3±5.5	14.6±6.8	0.058
Albumin (g/L)	29.5±10.6	22.4±10.3	34.2±7.8	<0.001□
Creatinine (μmol/L)	82.6±17.7	80.2±13.4	84.3±20.0	0.185
Cystatin C (mg/L)	1.0±0.3	1.0±0.3	1.0±0.3	0.428
Total Cholesterol (mmol/L)	6.6±2.6	8.3±2.9	5.4±1.6	<0.001□
TG (mmol/L)	1.9±1.2	2.4±1.3	1.6±1.1	<0.001□
HDL-C (mmol/L)	1.4±0.5	1.6±0.6	1.3±0.4	0.003□
LDL-C (mmol/L)	4.3±1.8	5.5±2.0	3.5±1.1	<0.001□
ApoA1 (g/L)	1.3±0.4	1.4±0.5	1.2±0.4	0.088
ApoB (g/L)	1.3±0.5	1.6±0.6	1.0±0.3	<0.001□
24 h UPE (g/24h)	1.1 (0.2-4.2)	4.2 (1.0-10.2)	0.4 (0.1-1.8)	<0.001□
eGFR (ml/min/1.73m^2)	89.4±19.7	95.5±19.6	85.4±18.9	0.006□
Treatment with RASI, *n* (%)	34 (28.8)	18 (38.3)	16 (22.5)	0.064
Treatment with glucocorticoids, *n* (%)	37 (31.4)	23 (48.9)	14 (19.7)	0.001□
Infection, *n* (%)	34 (28.8)	16 (34.0)	18 (25.4)	0.308

**P* value was assessed between Vitamin D deficient group and Vitamin D nondeficient by *t*-test, Mann-Whitney U-test or Chi-square test; □Statistically significant. Results are presented as mean±SD, median (IQR) or *n* (%). SBP=Systolic blood pressure; DBP=Diastolic blood pressure; 25(OH) D=25-hydroxyvitamimn D; AST=Aspartate transaminase; ALT=Alanine transaminase; GGT=Gamma-glutamyl transpeptidase; BALP=Bone alkaline phosphatase; ALP=Alkaline phosphatase; TG=Triglyceride; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; UPE=Urinary protein excretion; eGFR=Estimated glomerular filtration rate; RASI=Renin angiotensin system inhibitors; IQR=Interquartile range; SD=Standard deviation

Table 2: Associated factors of Vitamin D deficiency in patients with stages 1 and 2 chronic kidney disease

Characteristic	OR (95% CI)	P*
High serum level of GGT	5.163 (1.105-24.130)	0.037□
Serum albumin <30.0 g/L	1.727 (0.497-5.995)	0.390
Dyslipidemia	3.083 (1.029-9.243)	0.044□
24 h UPE ≥3.5 g/24 h	5.010 (1.316-19.074)	0.018□
eGFR ≥90 ml/min/1.73m^2	2.628 (0.989-6.984)	0.053
Treatment with glucocorticoids	2.973 (1.093-8.084)	0.033□

**P* value was assessed using multivariate binary logistic regression analysis, □Statistically significant. CKD=Chronic kidney disease; GGT=Gamma-glutamyl transpeptidase; UPE=Urinary protein excretion; eGFR=Estimated glomerular filtration rate; OR=Odds ratio; CI=Confidence interval

membranous nephropathy (MN) (19/118, 16.1%), minimal change disease (MCD) (14/118, 11.9%), focal segmental glomerulosclerosis (FSGS) (5/118, 4.2%), mesangial proliferative nephritis (2/118, 1.7%), lupus nephritis (LN) (14/118, 11.9%), diabetes nephropathy (DN) (7/118, 5.9%), hypertension (3/118, 2.5%), Henoch-Schonlein purpura (1/118, 0.8%), hepatitis B infection (2/118, 1.7%), vasculitis (1/118,0.8%), obstructive nephropathy (1/118, 0.8%) gout (1/118, 0.8%), Sjogren syndrome (1/118, 0.8%), and CKDs with uncertain diagnosis or others (23/118, 19.5%). None of the patients were on vitamin D analogues. Study participants' characteristics are shown in Table 1.

Table 3: Comparison of major characteristics among different types of nephropathy in patients with stages 1 and 2 chronic kidney disease

Characteristic	MCD (*n*=14)	MN (*n*=19)	IgAN (*n*=24)	FSGS (*n*=5)	LN (*n*=14)	DN (*n*=7)	*P**
25(OH) D (nmol/L)	24.1±16.1	32.3±13.9	53.5±16.7	46.6±11.5	37.1±17.3	41.4±14.6	<0.001□
Vitamin D deficiency, *n* (%)	12 (85.7)	12 (63.2)	3 (12.5)	1 (20.0)	7 (50.0)	2 (28.6)	<0.001□
Serum GGT (U/L)	19.0 (14.0-39.8)	38.0 (20.0-57.0)	15.5 (12.3-30.3)	26.0 (13.5-50.5)	20.0 (18.0-46.5)	63.0 (15.0-96.0)	0.037□
Total cholesterol (mmol/L)	9.7±2.6	8.6±2.3	5.0±1.1	6.8±3.6	5.5±1.7	5.0±1.7	<0.001□
24 h UPE (g/24 h)	8.5 (3.4-17.5)	4.2 (1.8-7.8)	0.3 (0.1-0.8)	0.2 (0.1-3.0)	0.7 (0.1-4.5)	1.6 (0.2-2.2)	<0.001□
Treatment with glucocorticoids, *n* (%)	9 (64.3)	5 (26.3)	3 (12.5)	1 (20.0)	12 (85.7)	1 (14.3)	<0.001□

**P* value was assessed among different types of nephropathy by One-way ANOVA, Kruskal-Wallis test or Chi-square test, □Statistically significant. Results are presented as mean±SD, median (IQR) or n (%). MCD=Minimal change disease; MN=Membranous nephropathy; IgAN=IgA nephropathy; FSGS=Focal segmental glomerular sclerosis; LN=Lupus nephritis; DN=Diabetic nephropathy; 25(OH)D=25-hydroxyvitamimn D; GGT=Gamma-glutamyl transpeptidase; UPE=Urinary protein excretion; IQR=Interquartile range; SD=Standard deviation

Serum 25 (OH) D level and associated factors of vitamin D deficiency

The mean serum 25 (OH) D level was 43.0 ± 20.1 nmol/L in this population, of which nine (7.6%) had normal serum 25 (OH) D level, 62 (52.5%) were in vitamin D insufficient state while the remaining 47 (39.8%) were in vitamin D deficient state. Depending on the serum 25 (OH) D levels, patients were divided into two groups, vitamin D deficient and non-deficient groups, with the cutoff value of 37 nmol/L. As shown in Table 1, the patients in the vitamin D deficient group had lower serum albumin levels ($P < 0.001$). The levels of serum GGT ($P = 0.004$), CHOL ($P < 0.001$), TG ($P < 0.001$), HDL-C ($P = 0.003$), LDL-C ($P < 0.001$), and ApoB ($P < 0.001$) were higher in the vitamin D deficient group. In addition, patients with vitamin D deficiency had a higher amount of 24-hour UPE ($P < 0.001$) and a higher eGFR ($P = 0.006$). The vitamin D deficient group had a higher proportion of patients on glucocorticoids than the vitamin D non-deficient group ($P = 0.001$).

The variables that showed significant differences between the two groups were considered potential associated factors of vitamin D deficiency and selected for further analysis. The serum GGT >60.0 U/L was defined as a high serum level of GGT. The patients who met one of the following criteria: serum CHOL >6.0 mmol/L, serum TG >2.3 mmol/L, serum LDL-C >3.6 mmol/L, or serum ApoB >1.1 g/L were diagnosed with dyslipidemia. By multivariate binary logistic regression analysis, high serum levels of GGT (OR = 5.163; 95% CI, 1.105-24.130; $P = 0.037$), dyslipidemia (OR = 3.083; 95% CI, 1.029-9.243; $P = 0.044$), 24-hour UPE ≥ 3.5 g/24 hrs (OR = 5.010; 95% CI, 1.316-19.074; $P = 0.018$), and treatment with glucocorticoids (OR = 2.973; 95% CI, 1.093-8.084; $P = 0.033$) were independent associated factors of vitamin D deficiency as shown in Table 2.

Vitamin D deficiency in different types of nephropathy

Depending on the different pathological types of nephropathy, 83 patients were divided into six groups: MCD, MN, IgAN, FSGS, LN, and DN. The patients with the rare types of nephropathy (fewer than five cases) in our study and with uncertain diagnosis were not included in this analysis.

As shown in Table 3, the incidence of vitamin D deficiency was significantly different among the different types of nephropathy ($P < 0.001$), with MCD having the highest incidence (12/14, 85.7%). The levels of serum 25 (OH) D ($P < 0.001$), serum GGT ($P = 0.037$), serum total CHOL ($P < 0.001$), 24-hour UPE ($P < 0.001$), and the usage rate of glucocorticoids ($P < 0.001$) were significantly different among the different nephropathies. Among the six types of nephropathy, MCD had the lowest serum 25 (OH) D level, highest serum total CHOL and 24-hour UPE levels.

Discussion

We conducted an observational single-center study to evaluate the vitamin D status and the factors associated with vitamin D deficiency in patients with stages 1 and 2 CKD in southern China. We found that almost 92.4% of CKD patients with normal kidney function were in a poor vitamin D state, of whom 39.8% were in vitamin D deficient state. We also discovered that high serum GGT levels, dyslipidemia, 24-hour UPE ≥3.5 g/24 hrs, and treatment with glucocorticoids were independent associated factors of vitamin D deficiency in stages 1 and 2 CKD patients. Among different types of nephropathy, MCD had the highest incidence of vitamin D deficiency.

Poor vitamin D status, including vitamin D insufficiency and deficiency, is a common problem worldwide. It has been reported that in the general healthy population, around 30%-80% people have low serum 25 (OH) D concentration. The notable differences in prevalence,

reported in different studies, are due to the diversity of race, district, season, food intake, age, and other factors.[3,9,10] In patients with CKD, most of the observations of vitamin D insufficiency and deficiency were focused on stage 3-5 CKD, with the prevalence of more than 80%.[6,8,11-13] KDIGO guidelines also suggest monitoring serum 25 (OH) D levels in stage 3-5 CKD patients.[4] In our study, we observed that 92.4% of stages 1 and 2 CKD patients had low serum 25 (OH) D concentration, of whom 39.8% had vitamin D deficiency and the other 52.5% had vitamin D insufficiency. According to our results, we revealed that the incidence of poor vitamin D status is also high in CKD patients, even with normal renal function, which may support the necessity to detect serum 25 (OH) D level in this population and to prescribe vitamin D supplementation due to the poor outcome of vitamin D deficiency.[5,6]

According to our results, we found that the high serum level of GGT was one of the independent associated factors of vitamin D deficiency in patients with stages 1 and 2 CKD. 1,25-dihydroxyvitamin D3 was reported to play a role in regulating the synthesis and activity of GGT.[14,15] Further investigation is necessary to determine whether there is feedback of GGT to serum vitamin D and its possible mechanism.

Previously, serum 25 (OH) D level was reported to inversely correlate with the levels of serum total CHOL, TG, and non-HDL CHOL.[16,17] In our study, the serum total CHOL, TG, and non-HDL were observed to be higher in the vitamin D deficient group. Moreover, dyslipidemia was found to be independently associated with vitamin D deficiency. Our study corroborates the findings of others as mentioned above and suggests that vitamin D deficiency may induce dyslipidemia. The potential mechanism is still under investigation. It is reported that vitamin D can increase the efficiency of the intestinal calcium absorption,[3] and that calcium could reduce the serum level of CHOL by promoting the conversion of CHOL into bile acids.[18] In addition, the increasing absorption of intestinal calcium could inhibit the synthesis and secretion of hepatic TG.[19] Furthermore, increased levels of intestinal calcium could also reduce serum levels of LDL-C by decreasing the absorption of fatty acids.[20] Therefore, vitamin D may influence the serum lipid profile through stimulating the intestinal calcium absorption.

In previous studies, vitamin D deficiency was reported to be inversely correlated with the amount of urinary protein in CKD patients before.[5,8,13] In our study, the 24-hour UPE ≥3.5 g/24 hrs was found to be independently associated with vitamin D deficiency. It should be explained that nearly all circulating vitamin D (85-90%) is bound to vitamin D-binding protein (DBP), with a small proportion bound to albumin.[21] Serum DBP and albumin may also leak from the glomerular filtration membrane with other proteins when glomerulonephropathies exist. Serum vitamin D concentration decreases as a result of serum protein leakage.

Whether vitamin D deficiency is associated with the treatment with glucocorticoids is still controversial.[22,23] In our study, vitamin D deficiency was observed to be independently associated with the treatment using glucocorticoids. It has been reported that the catabolism of vitamin D can be accelerated by glucocorticoids,[24] which may explain the high usage rate of glucocorticoids in the vitamin D deficient group. In order to treat and prevent vitamin D deficiency, vitamin D supplementation is suggested in CKD patients receiving treatment with glucocorticoids.

The incidence of vitamin D deficiency in different types of nephropathy has seldom been reported earlier. A study on advanced CKD revealed that low vitamin D status is characteristically associated with advanced diabetic nephropathy.[25] In another study, a higher rate of glomerular diagnosis was reported in the vitamin D deficient group compared to the vitamin D non-deficient group.[26] Among the different types of nephropathy in our study, including MCD, MN, IgAN, FSGS, LN and DN, MCD had the highest incidence of vitamin D deficiency. This may be due to the highest amount of 24-hour UPE observed in the MCD group as shown in Table 3.

Conclusion

Poor vitamin D status is common in patients with stages 1 and 2 CKD with a 39.8% incidence of vitamin D deficiency, which may support the necessity to detect serum 25 (OH) D levels in CKD patients, even with normal renal function. High serum GGT level, dyslipidemia, 24-hour UPE ≥3.5 g/24 hrs, and treatment with glucocorticoids are independent associated factors of vitamin D deficiency, which may be alerts of vitamin D deficiency for physicians.

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Conflicts of interest

There are no conflicts of interest.

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