Original Article

Predictors of Vitamin D Deficiency in Predialysis Patients with Stage 3–5 Chronic Kidney Diseases in Southern China

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Abstract

Objective: Vitamin D status and risk factors of Vitamin D deficiency in chronic kidney disease (CKD) patients in China have been seldom reported before. In this study, we aim to investigate serum 25-hydroxyvitamin D [25(OH)D] status and find the predictors of Vitamin D deficiency in predialysis patients with Stage 3–5 CKDs in Southern China. **Methods:** In this retrospective cross-sectional study, hospitalized predialysis patients who were diagnosed of Stage 3–5 CKD and had taken measurement of serum 25(OH)D in a single center from January 2014 to June 2015 were included. Patients were divided into Vitamin D deficiency group and nondeficiency group depending on the cutoff serum 25(OH)D value of 37 nmol/L. Clinical and biochemical parameters were collected and evaluated for predictors of Vitamin D deficiency by logistic regression. **Results:** One hundred and fifty-two patients were included in this study, of which 87 (57.2%) were in Vitamin D insufficiency state while 60 (39.5%) were in Vitamin D deficiency state. Serum 25(OH)D levels of patients in Stage 4 and Stage 5 CKD were lower than that of patients in Stage 3 CKD ($P = 0.002$). It was discovered that female gender (odds ratio [OR] = 3.674; 95% confidence interval [CI], 1.607–8.396; $P = 0.002$), serum albumin level <30.0 g/L (OR = 6.816; 95% CI, 2.634–17.633; $P < 0.001$), and estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (OR = 4.761; 95% CI, 1.353–16.754; $P = 0.015$) were independent predictors of Vitamin D deficiency. **Conclusions:** Vitamin D insufficiency and deficiency are common in predialysis patients with Stage 3–5 CKD in Southern China. Female gender, hypoalbuminemia with serum albumin level <30.0 g/L, and severe damaged renal function with eGFR <30 ml/min/1.73 m^2 are independent predictors of Vitamin D deficiency in predialysis patients with Stage 3–5 CKD.

Keywords: *Chronic kidney disease, predialysis, predictors, Vitamin D deficiency*

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Introduction

25-hydroxyvitamin D [25(OH)D] is the major circulating form of Vitamin D and stands for body store of Vitamin D.[1] Low serum 25(OH)D level is common in patients with chronic kidney diseases (CKD), especially in Stage 3–5 CKD.[2] According to 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, serum 25(OH)D level of 15–30 ng/mL (1 ng/mL is equivalent to 2.5 nmol/L) is defined as Vitamin D insufficiency, while serum 25(OH)D level <15 ng/mL as Vitamin D deficiency.[1] The prevalence of Vitamin D insufficiency and deficiency increases as kidney function declines in CKD patients.[2-4] More and more evidence suggests that Vitamin D deficiency is not only associated with CKD-mineral and bone disorders but also linked to increased cardiovascular and cerebrovascular risks, cancer, autoimmune, and infectious diseases.[5-9] Besides, it has been reported that low 25(OH)D level is correlated with increased all-cause

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and cardiovascular mortality in CKD patients.[10-12] It might be speculated that correction of the low serum 25(OH)D status might improve the outcome of CKD patients.

Due to the important role of Vitamin D in CKD patients, monitoring serum 25(OH)D concentration is suggested in Stage 3–5 CKD patients by KDIGO guidelines.[1] Vitamin D status and risk factors with Vitamin D deficiency in CKD patients in China have been seldom reported. In this study, we aim to investigate serum 25(OH)D status and find the predictors of Vitamin D deficiency in predialysis patients with Stage 3–5 CKD in Southern China.

Methods

Study design and population

This was a retrospective cross-sectional study including hospitalized patients in Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Guangzhou, China, from January 2014 to June 2015. Patients who met the following criteria were included (a) had taken measurement of serum 25(OH)D; (b) were diagnosed of chronic kidney disease according to KDIGO guidelines;[13] (c) with the estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2; and (d) not under hemodialysis or peritoneal dialysis. Patients <14 years old were excluded.

Study setting

Serum 25(OH)D level ≥75 nmol/L was defined as normal, of 37–75 nmol/L as Vitamin D insufficiency while <37 nmol/L as Vitamin D deficiency.[1] Depending on the level of serum 25(OH)D, patients were divided into Vitamin D deficiency group and nondeficiency group with the cutoff value of 37 nmol/L. Patients' demographic information, laboratory data, diagnosis, treatments underwent, and complications were collected. The blood pressure and laboratory data measured within 7 days before or after the date when serum 25(OH)D sample was taken were gathered for the research.

Ethical considerations

This study was conducted in compliance with the Declaration of Helsinki and the Ethical Standards of the Research Committee in Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China.

Laboratory assays

Serum 25(OH)D and bone alkaline phosphatase (ALP) were measured by enzyme immunoassay according to the protocols of the kits (Immunodiagnostic Systems, UK). Serum intact parathyroid hormone (PTH) was measured by chemiluminescence with the matched reagent on ADVIA Centaur® XP Immunoassay System (Siemens, UK). Blood hemoglobin concentration was measured on XN-1000 automatic analyzer (Sysmex, Japan). Serum ALP, calcium, phosphorus, iron, albumin, creatinine, cystatin C, total cholesterol (CHOL), triglyceride, high-density lipoprotein-CHOL, low-density lipoprotein-CHOL, apolipoprotein (Apo) A1 and ApoB were measured on AU5800 automatic biochemistry analyzer (Beckman Coulter, US) using matched reagents according to the manufacturer's instructions. Serum corrected calcium was calculated by the formula (serum corrected calcium [mmol/L] = measured serum calcium −0.02 × [serum albumin−40]). Serum ferritin was detected by chemiluminescence with the kit (Siemens, UK). Three independent urine samples were measured by immunoturbidimetric assay with reagent (Leadman, China) for 24-h urinary protein excretion, and the average value of the three measurements was adopted.

Other covariates

Blood pressure was measured with a brachial sphygmomanometer three times after the participant had rested in the supine position for at least 10 min, and the average value of the three measurements was adopted. eGFR was calculated by the CKD- EPI cystatin and creatinine 2012 equation.[13] Being under the treatment before the measurement of serum 25(OH) D with renin-angiotensin system inhibitors including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, statins, and Vitamin D analogues were recorded.

Statistical analysis

Categorical data are presented as numbers and percentages while continuous variables as means ± standard deviations (normally distributed variables) or as medians with interquartile range (skewed variables). Categorical variables were compared using the Chi-square test. Comparisons between continuous variables were performed by *t*-test (normally distributed variables) or Mann–Whitney U-test (skewed variables). Pearson's bivariate correlation (normally distributed variables) or Spearman's bivariate correlation (skewed variables) was used to assess the strength of the associations between the analyzed data and the serum 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 (forward: Conditional method). All statistical tests were two sided and $P < 0.05$ was considered statistically significant. All of the statistical analyses were performed with GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA) or SPSS version 19.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

One hundred and fifty-two predialysis CKD patients with eGFR <60 ml/min/1.73 m^2 were included in this study. Twenty-seven (17.8%) patients were in CKD Stage 3, 39 (25.7%) patients were in CKD Stage 4 while the left 86 (56.6%) were in Stage 5. Mean serum 25(OH)D level was (43.0 ± 17.3) nmol/L in this group of patients, of which 5 (3.3%) patients had normal serum 25(OH)D concentration, 87 (57.2%) were in Vitamin D insufficiency state while the left 60 (39.5%) were in Vitamin D deficiency state. Both serum 25(OH)D levels of patients in Stage 4 CKD ([43.2 ± 17.3] nmol/L) and Stage 5 CKD ([39.2 ± 14.5] nmol/L) were lower than that of patients in Stage 3 CKD ([52.1 ± 18.1] nmol/L) (P = 0.002) [Figure 1]. Primary diseases of this group of patients were shown in Table 1.

Predictors of Vitamin D deficiency

As shown in Table 2, patients in Vitamin D deficiency group had higher female proportion (60.0% vs.

Table 1: Primary diseases of predialysis patients with Stage 3-5 chronic kidney diseases in Southern China (n=152)

Primary disease	Overall, n (%)
Primary glomerulonephritis	52 (34.2)
Diabetic nephropathy	39 (25.7)
Hypertensive nephropathy	31 (20.4)
Obstructive nephropathy	10 (6.6)
Gouty nephropathy	6 (3.9)
Polycystic kidney	4 (2.6)
Lupus nephritis	3 (2.0)
Chronic interstitial nephritis	2 (1.3)
Vasculitis	2 (1.3)
HBV-related nephritis	1 (0.7)
Sjogren's syndrome	1 (0.7)
Chronic pyelonephritis	1 (0.7)

HBV=Hepatitis B virus

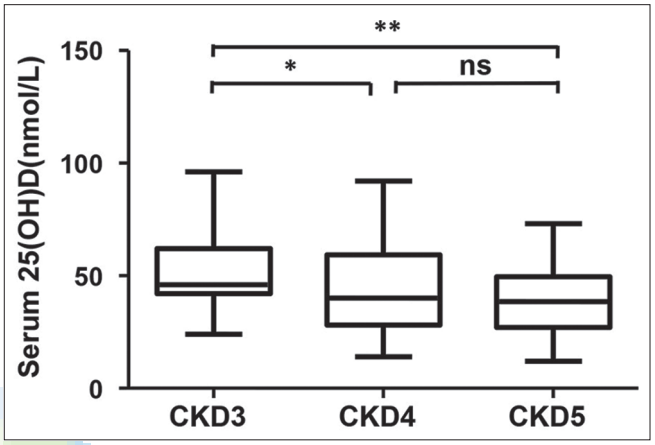

Figure 1: Serum 25-hydroxyvitamin D levels in patients with both Stage 4 and Stage 5 chronic kidney disease were significantly lower than that in patients with Stage 3 chronic kidney disease. *P < 0.05, **P < 0.01

Table 2: Comparison of clinical and biochemical characteristics between Vitamin D deficiency group and nondeficiency group in Stage 3-5 predialysis chronic kidney diseases patients

Characteristic	Vitamin D deficiency 25(OH) D <37 nmol/L (n=60)	Vitamin D nondeficiency 25(OH) D ≥37 nmol/L (n=92)	P*
Age (years)	59.3±15.7	56.3±14.4	0.239
Female gender, n (%)	36 (60.0)	38 (41.3)	0.024†
Diabetic nephropathy, n (%)	22 (36.7)	27 (29.3)	0.345
Systolic blood pressure (mmHg)	146.8±17.0	144.6±19.5	0.470
Diastolic blood pressure (mmHg)	81.3±12.9	84.6±13.3	0.128
Hemoglobin (g/L)	92.9±19.0	105.0±22.9	<0.001†
Serum parameters			
25(OH)D (nmol/L)	27.2±6.2	53.3±14.3	<0.001†
BALP (μg/L)	14.0 (11.0-19.8)	16.5 (12.0-21.8)	0.430
ALP (U/L)	82.2±34.7	84.2±29.1	0.703
Corrected calcium (mmol/L)	2.3±0.2	2.3±0.1	0.404
Phosphorus (mmol/L)	1.6±0.5	1.4±0.3	0.015†
Intact-PTH (pg/ml)	115.5 (47.3-272.5)	72.0 (39.0-163.3)	0.042†
Iron (μmol/L)	11.4±5.7	12.7±5.8	0.155
Albumin (g/L)	31.6±6.6	35.1±5.1	<0.001†
Creatinine (μmol/L)	423.4±235.5	352.6±198.8	0.048†
Cystatin C (mg/L)	3.1 (2.5-3.9)	2.8 (2.2-3.9)	0.122
Total cholesterol (mmol/L)	5.1±1.3	4.9±1.3	0.240
Triglyceride (mmol/L)	2.0±1.6	1.9±1.5	0.713
HDL-C (mmol/L)	1.2±0.4	1.1±0.3	0.115
LDL-C (mmol/L)	3.0±0.8	2.9±0.8	0.348

Contd...

Table 2: Contd...

Characteristic	Vitamin D deficiency 25(OH) D <37 nmol/L (*n*=60)	Vitamin D nondeficiency 25(OH) D ≥37 nmol/L (*n*=92)	*P**
ApoA1 (g/L)	1.2±0.2	1.1±0.2	0.216
ApoB (g/L)	1.0±0.3	0.9±0.3	0.095
Ferritin (ng/ml)	231.5 (98.1-435.8)	206.9 (91.2-360.8)	0.820
24-h urinary protein excretion (g/24 h)	1.9 (0.7-4.0)	1.2 (0.6-2.6)	0.103
eGFR (ml/min/1.73 m^2)	14.4±8.2	21.1±14.9	0.002†
Treatment, *n* (%)			
RAS inhibitor	12 (20.0)	26 (28.3)	0.250
β-blocker	21 (35.0)	32 (34.8)	0.978
Statin	12 (20.0)	12 (13.0)	0.250
Vitamin D analog	10 (16.7)	8 (8.7)	0.137
Complications, *n* (%)			
Cardiac valvular calcification	8 (13.3)	13 (14.1)	0.889
Infection	16 (26.7)	18 (19.6)	0.304

Results are presented as mean±SD, median (interquartile range) or *n* (%). **P* value was assessed using *t*-test, Mann–Whitney U-test or Chi-square test, †Statistically significant. 25(OH)D=25-hydroxyvitamimn D; BALP=Bone alkaline phosphatase; ALP=Alkaline phosphatase; PTH=Parathyroid hormone; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; eGFR=Estimated glomerular filtration rate; RAS=Renin angiotensin system; SD=Standard deviation

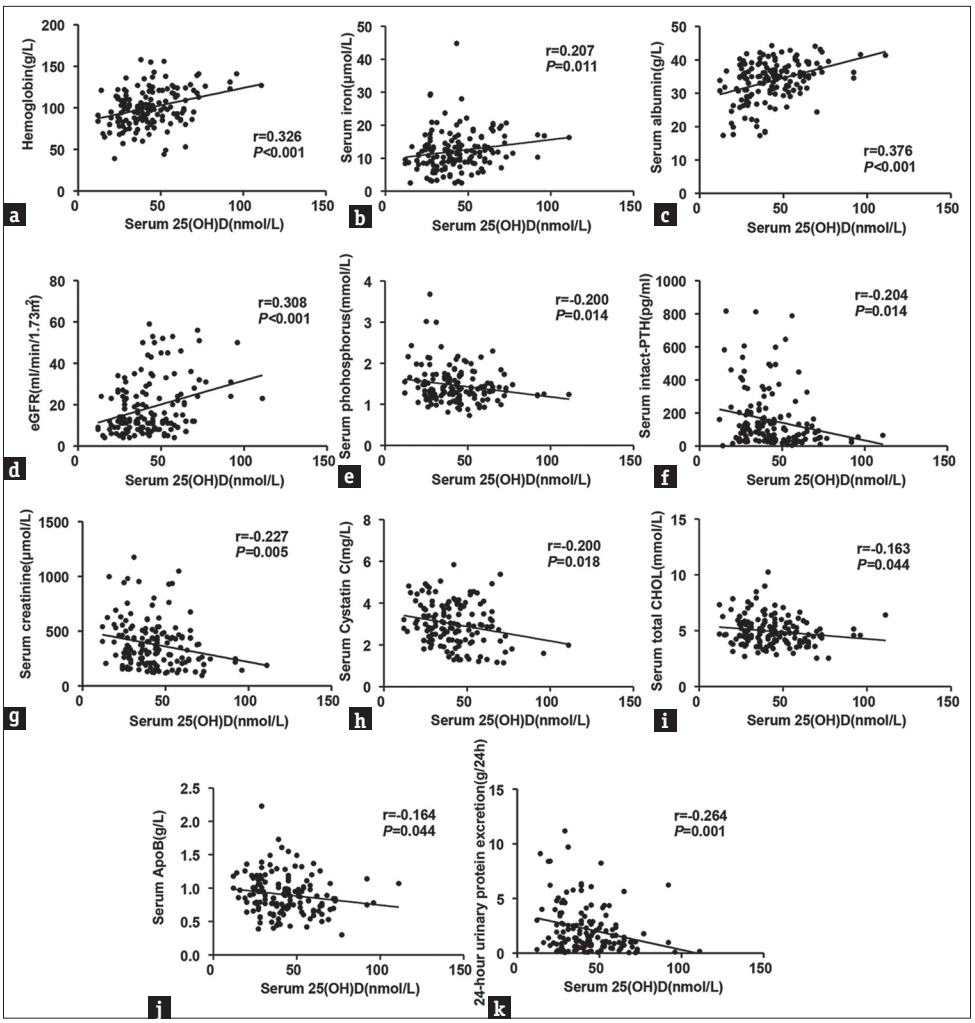

Figure 2: Serum 25-hydroxyvitamin D level was positively correlated with hemoglobin concentration (a), serum iron level (b), serum albumin level (c), and estimated glomerular filtration rate (d), whereas inversely correlated with serum phosphorus level (e), serum intact parathyroid hormone level (f), serum creatinine level (g), serum cystatin C level (h), serum total cholesterol level (i), serum apolipoprotein B level (j), and 24-h urinary protein excretion level (k)

41.3%, $P = 0.024$), lower hemoglobin concentration ([92.9 ± 19.0] g/L vs. [105.0 ± 22.9] g/L, $P < 0.001$), higher serum phosphorus level ([1.6 ± 0.5] mmol/L vs. [1.4 ± 0.3] mmol/L, $P = 0.015$), higher serum intact-PTH level (115.5 [47.3–272.5] pg/ml vs. 72.0 [39.0–163.3] pg/ml, $P = 0.042$), lower serum albumin level ([31.6 ± 6.6] g/L vs. [35.1 ± 5.1] g/L, $P < 0.001$), higher serum creatinine level ([423.4 ± 235.5] μmol/L vs. [352.6 ± 198.8] μmol/L, $P = 0.048$) and lower eGFR ([14.4 ± 8.2] ml/min/1.73 m^2 vs. [21.1 ± 14.9] ml/min/1.73 m^2, $P = 0.002$).

Table 3: Bivariate correlation of serum 25-hydroxyvitamimn D level with clinical and biochemical parameters in Stage 3-5 predialysis chronic kidney diseases patients

Characteristic	*r**	*P*
Age (years)	−0.095	0.243
Systolic blood pressure (mmHg)	−0.096	0.237
Diastolic blood pressure (mmHg)	0.133	0.104
Hemoglobin (g/L)	0.326	<0.001†
Serum parameters		
BALP (μg/L)	−0.014	0.866
ALP (U/L)	0.010	0.906
Corrected calcium (mmol/L)	0.037	0.648
Phosphorus (mmol/L)	−0.200	0.014†
Intact-PTH (pg/ml)	−0.204	0.014†
Iron (μmol/L)	0.207	0.011†
Albumin (g/L)	0.376	<0.001†
Creatinine (μmol/L)	−0.227	0.005†
Cystatin C (mg/L)	−0.200	0.018†
Total cholesterol (mmol/L)	−0.163	0.044†
Triglyceride (mmol/L)	−0.094	0.248
HDL-C (mmol/L)	−0.116	0.156
LDL-C (mmol/L)	−0.134	0.101
ApoA1 (g/L)	−0.064	0.436
ApoB (g/L)	−0.164	0.044†
Ferritin (ng/ml)	−0.016	0.845
24-h urinary protein excretion (g/24 h)	−0.264	0.001†
eGFR (ml/min/1.73 m^2)	0.308	<0.001†

*Results were assessed using Pearson's bivariate correlation or Spearman's bivariate correlation, †Statistically significant. 25(OH)D=25-hydroxyvitamimn D; BALP=Bone alkaline phosphatase; ALP=Alkaline phosphatase; PTH=parathyroid hormone; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; eGFR=Estimated glomerular filtration rate

As shown in Table 3 and Figure 2, serum 25(OH)D level was positively correlated with hemoglobin concentration ($r = 0.326$, $P < 0.001$) [Figure 2a], serum iron level ($r = 0.207$, $P = 0.011$) [Figure 2b], serum albumin level ($r = 0.376$, $P < 0.001$) [Figure 2c], and eGFR ($r = 0.308$, $P < 0.001$) [Figure 2d] whereas inversely correlated with serum phosphorus level ($r = −0.200$, $P = 0.014$) [Figure 2e], serum intact-PTH level ($r = −0.204$, $P = 0.014$) [Figure 2f], serum creatinine level ($r = −0.227$, $P = 0.005$) [Figure 2 g], serum cystatin C level ($r = −0.200$, $P = 0.018$) [Figure 2 h], serum total CHOL level ($r = −0.163$, $P = 0.044$) [Figure 2i], serum ApoB level ($r = −0.164$, $P = 0.044$) [Figure 2j], and 24-h urinary protein excretion level ($r = −0.264$, $P = 0.001$) [Figure 2k].

Based on the above results, variables of female gender, hemoglobin <90.0 g/L, serum phosphorus >1.6 mmol/L, serum intact-PTH >67.0 pg/ml, serum iron <7.0 μmol/L, serum albumin <30.0 g/L, serum total CHOL >6.0 mmol/L, serum ApoB >1.1 g/L, 24-h urinary protein excretion ≥3.5 g/24 h, and eGFR <30 ml/min/1.73 m^2 were regarded as the potential risk factors of Vitamin D deficiency. By multivariate binary logistic regression analysis (forward: Conditional method), only female gender, serum albumin level <30.0 g/L, and eGFR <30 ml/min/1.73 m^2 were in the equation. Female gender (odds ratio [OR] = 3.674; 95% confidence interval [CI], 1.607–8.396; $P = 0.002$), serum albumin level <30.0 g/L (OR = 6.816; 95% CI, 2.634–17.633; $P < 0.001$), and eGFR <30 ml/min/1.73 m^2 (OR = 4.761; 95% CI, 1.353–16.754; $P = 0.015$) were independent predictors of Vitamin D deficiency as shown in Table 4.

Table 4: Predictors of Vitamin D deficiency in Stage 3–5 predialysis chronic kidney diseases patients

Characteristic	OR (95% CI)	*P**
Female gender	3.674 (1.607-8.396)	0.002†
Hemoglobin <90.0 g/L	-	0.241
Serum phosphorus >1.6 mmol/L	-	0.147
Serum Intact-PTH >67.0 pg/ml	-	0.215
Serum iron <7.0 μmol/L	-	0.534
Serum albumin <30.0 g/L	6.816 (2.634-17.633)	<0.001†
Serum total cholesterol >6.0 mmol/L	-	0.718
Serum ApoB >1.1 g/L	-	0.771
24-h urinary protein excretion ≥3.5g/24 h	-	0.214
eGFR <30 ml/min/1.73 m^2	4.761 (1.353-16.754)	0.015†

**P* value was assessed using multivariate binary logistic regression analysis (Forward: Conditional method), †Statistically significant. OR=odds ratio; CI=Confidence interval; eGFR=Estimated glomerular filtration rate; PTH=parathyroid hormone

Discussion

In this study, we conducted a retrospective cross-sectional single-center study to evaluate the Vitamin D status and the predictors of Vitamin D deficiency in predialysis patients with Stage 3–5 CKD in Southern China. We found that 96.7% of this patients had low serum 25(OH)D concentration, and serum 25(OH)D concentration decreased significantly from Stage 4 CKD onward. We also discovered that higher proportion of female gender, lower hemoglobin level, higher serum phosphorus level, higher serum intact-PTH level, lower serum albumin level, higher serum creatinine level, and lower eGFR were found in Vitamin D deficiency group. Furthermore, serum 25(OH)D level was found to be positively correlated with hemoglobin, serum iron level, serum albumin level, and eGFR whereas inversely correlated with serum phosphorus level, serum intact-PTH level, serum creatinine level, serum cystatin C level, serum total CHOL level, serum ApoB level, and 24-h urinary protein excretion. Among the potential risk factors mentioned above, female gender, serum albumin <30.0 g/L, and eGFR <30 ml/min/1.73 m^2 were independent predictors for Vitamin D deficiency.

Vitamin D insufficiency and deficiency were reported to occur in more than 80% of Stage 3–5 CKD patients in both Western and other Asian countries.[4,14,15] In our study, we observed that 96.7% of predialysis patients with Stage 3–5 CKD had low serum 25(OH)D level in Southern China, which was similar with the studies reported in other regions.[4,14,15]

In general population, women especially those who were pregnant, lactating, or postmenopausal were at high risk of Vitamin D deficiency.[3] In CKD patients, women were also at higher risk to suffer from Vitamin D deficiency compared to men.[10] In our study, we found that female gender was an independent risk factor of Vitamin D deficiency in predialysis Stage 3–5 CKD patients, which was consistent with the studies of general population or other CKD population mentioned above.

Being consistent with other studies in CKD patients reported before,[11,16,17] hypoalbuminemia was found to be an independent risk factor of Vitamin D deficiency in our study. It should be explained that a proportion of circulating Vitamin D bounds to albumin[18] and that serum Vitamin D concentration decreases as a result of serum albumin level declines. It may be deduced that to increase the serum albumin level may contribute to correction of Vitamin D inadequacy.

Serum 25(OH)D level was reported to decline as eGFR decreased.[4,14,15] In our study, we found that serum 25(OH)D level declined significantly from Stage 4 of CKD (eGFR <30 ml/min/1.73 m^2) onward, and what's more, eGFR <30 ml/min/1.73 m^2 was an independent predictor of Vitamin D deficiency. It has been reported that the prevalence of Vitamin D deficiency was increased dramatically from Stage 4 of CKD onward, with relatively low prevalence in both Stages 3a and 3b of CKD.[4] What we found in our study was consistent with the result of the study mentioned above, but the independent predictor role of eGFR <30 ml/min/1.73 m^2 has not been pointed out elsewhere. It may be implied that monitoring serum 25(OH)D should be more active especially when eGFR decreases below 30 ml/min/1.73 m^2.

Conclusions

Vitamin D insufficiency and deficiency are common in predialysis patients with Stage 3–5 CKD in Southern China, which may support the necessity to detect serum 25(OH)D actively in this group of patients and make early diagnosis of Vitamin D insufficiency or deficiency.

Female gender, hypoalbuminemia with serum albumin level <30.0 g/L, and severe damaged renal function with eGFR <30 ml/min/1.73 m^2 are independent predictors of Vitamin D deficiency in predialysis patients with Stage 3–5 CKD. Physicians may have to be alert to those who are female, in hypoalbuminemia state or with severely decreased renal function to make early diagnosis of Vitamin D deficiency in predialysis patients with Stage 3–5 CKD.

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Conflicts of interest

There are no conflicts of interest.

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