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Original article

Prevalence of vitamin D deficiency in Thai patients receiving various modalities of renal replacement therapy

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Background: Vitamin D status of Thai patients receiving renal replacement therapy (RRT) is incompletely known.
Objectives: To determine the prevalence of vitamin D deficiency or insufficiency in adult Thai patients receiving various RRT modalities, and factors associated with low vitamin D levels.
Methods: In this retrospective, observational, single-center, cross-sectional study, we evaluated dialysis-related laboratory test variables from 111 patients receiving RRT. Serum 25-hydroxyvitamin D concentration [25(OH)D] <15 ng/mL was defined as deficiency, and 15–30 ng/mL as insufficiency.
Results: Low vitamin D levels were identified in 100% patients receiving peritoneal dialysis (PD; 81% deficient, 19% insufficient), 94% patients receiving online-hemodiafiltration (OL-HDF; 50% deficient, 44% insufficient), and 100% patients with kidney transplants (KT; 55% deficient, 45% insufficient). PD patients showed significantly lower serum [25(OH)D] than OL-HDF or KT patients (10.5 ± 5.9 vs 17.7 ± 8.5 vs 15.4 ± 6.1 ng/mL respectively, $P < 0.001$). OL-HDF patients with vitamin D deficiency had significantly lower vascular access flow than those without deficiency (833 ± 365 vs 1239 ± 385 mL/min, $P = 0.008$). KT recipients from deceased donors had lower serum [25(OH)D] than KT recipients from living, related donors (13.7 ± 6.0 vs 17.5 ± 5.7 ng/mL, $P = 0.045$). Multiple logistic regression found treatment by renin–angiotensin system blockade, serum triglyceride, and intact parathyroid hormone levels significantly associated with vitamin D deficiency after adjusting for sex, and serum calcium, phosphate, and albumin levels.
Conclusions: Nearly 100% patients receiving RRT had vitamin D deficiency or insufficiency, and RRT modalities might be related.

Keywords: prevalence, renal replacement therapy, vitamin D deficiency, 25 hydroxyvitamin D

Vitamin D has important roles in the function of various organs. Besides controlling calcium and bone homeostasis via the kidney, vitamin D regulates cell interaction, and modulates the immune response, thereby affecting susceptibility to infection via activation of vitamin D receptors expressed throughout the body [1]. Despite lacking renal 1α-hydroxylase, patients with chronic kidney disease (CKD) retain an ability to convert nutritional vitamin D or calcifediol (25-hydroxyvitamin D, 25(OH)D) to active vitamin D (1,25 $(OH)_2D$) using nonrenal 1α-hydroxylase present in several tissues including skin, breast, colon, prostate, and various cells in the immune system [2]. Therefore, an adequate quantity of 25(OH)D is necessary for production of 1,25 $(OH)_2D$. The best indicator of vitamin D status is serum concentration [25(OH)D] because it correlates with total body store, has a longer half-life, and has a higher blood concentration than 1,25 $(OH)_2D$ [3]. The U.S. National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/K/DOQI) Clinical Practice Guidelines suggest that replacement with 25(OH)D should be initiated before treatment with 1,25 $(OH)_2D$ in patients with CKD and a serum [25(OH)D] <30 ng/mL [4].

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Earlier studies reported the prevalence of 25(OH)D deficiency in as many as 30% to 80% of patients receiving renal replacement therapy (RRT) including hemodialysis (HD) [5-9], peritoneal dialysis (PD) [10-14], and post kidney transplantation (KT) [15-19] (**Table 1**).

However, to our knowledge there are no available studies that compare simultaneously the prevalence of 25(OH)D deficiency among adult patients receiving various modalities of RRT. 25(OH)D deficiency can cause detrimental effects in patients receiving dialysis including increased all-cause mortality [20, 21], long-term cardiovascular mortality because of atherosclerosis and endothelial dysfunction [22, 23], and a higher rate of hospitalization [24]. Similarly, KT recipient patients and low [25(OH)D] had higher rate of all-cause mortality, annual renal function decline, and development of acute cellular rejection [25-27].

The aims of the present study were to examine the impact of three different RRT modalities on serum [25(OH)D] in Thai patients simultaneously, and to assess factors that might affect vitamin D status.

Materials and methods

Study design and patients

The present study was a retrospective, observational, single tertiary center, cross-sectional study performed during June to July 2014 and was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 449/57). The study included data from 111 consecutive adult Thai patients who received either HD, PD, or KT at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, located at a latitude of just 13°43′N (suggesting strong exposure to sunlight). Demographic data including age, sex, comorbidity, dialysis vintage, and post-transplantation time were abstracted from a retrospective review of electronic medical records. No participants ever received oral ergocalciferol or cholecalciferol supplements.

Biochemical assays and laboratory measurement

Blood samples had been drawn midweek to obtain predialysis serum [25(OH)D], complete blood count, and calcium, phosphate, intact parathyroid hormone (iPTH), alkaline phosphatase, blood urea nitrogen (BUN), creatinine, uric acid, and albumin levels, lipid profile, and iron studies. Samples were immediately analyzed using standard automated methods. Serum [25(OH)D] was determined using a commercially available chemiluminescent immunoassay (DiaSorin Liaison, Stillwater, MN, USA). Interassay coefficient of variation (functional sensitivity) was 20% and the limit of detection was <4 ng/mL. According to the NKF/K/DOQI guidelines 25(OH)D deficiency is defined as <15 ng/mL, and insufficiency as 15–30 ng/mL, and sufficiency as >30 ng/mL. Total calcium (Ca) level was corrected using the equation: total Ca = serum Ca + [(4.0 – serum albumin) × 0.8]. Adequacy of dialysis was determined by using a urea kinetic model to achieve delivered Kt/V for HD patients. Total (renal and peritoneal) weekly Kt/V and total weekly creatinine clearance were assessed in patients receiving PD. Normalized protein nitrogen appearance (nPNA), representing daily protein intake, was derived from calculation of Kt/V, 24 h dialysate, and 24 h urine collection during a steady state. The renal dietitian routinely followed and monitored dialysis and KT recipients for body weight, height, body mass index (BMI) in conjunction with nutritional status assessment by the Malnutrition Inflammation Score.

Statistical analysis

All data are expressed as mean ± standard deviation (SD) while non-normally distributed variables are expressed as median with interquartile range (IQR). The statistical analysis was performed using SPSS Statistics for Windows, version 17.0 (SPSS Inc, Chicago, IL, USA). Differences between variables were compared using a one-way analysis of variance (ANOVA) and unpaired Student *t* tests for normally distributed variables. Kruskal–Wallis and Mann–Whitney *U* tests (Wilcoxon rank–sum test) were used to compare groups with non-normally distributed variables. Selected variables were analyzed by binary logistic regression with stepwise forward selection (data presented as [odds ratio (OR); 95% confidence interval (CI)]). $P < 0.05$ was considered significant.

Results

Patients characteristics and effects of different RRT modality on serum 25(OH)D level

We analyzed data from 111 patients who received on-line hemodiafiltration (OL-HDF, n = 32), PD (n = 37; continuous ambulatory PD, CAPD = 13 and automated PD, APD = 24) and KT (n = 42; KT deceased donor, DDKT = 23 and KT living, related donor, LRKT = 19). **Table 2** details baseline characteristics of the 3 RRT groups. Low vitamin D status was noted in 100% of patients receiving PD

Table 1. Summary of studies of prevalence of 25(OH)D deficiency in various renal replacement therapy modalities

Authors (year)	Countries	Study design	Population (n)	Duration of RRT (months)	Age (years)	[25(OH)D] (ng/mL)	Prevalence of low [25(OH)D] (ng/mL) %
Saab et al. [5] (2007)	USA	retrospective	HD (131)	66.5 [4–303]	59.0 [25–90]	16.9 ± 8.5	Deficient (<15) 51 Insufficient (<30) 92
Del Valle et al. [9] (2007)	Argentina	cross-sectional	HD (84)	41.0 ± 29.6	58.9 ± 16.6	24.4 (5–79)	Deficient (<15) 22.6 Insufficient (15–30) 53.5
Jean et al. [6] (2008)	France	cross-sectional	HD (253)	62 ± 74	66.7 ± 14	14.8 ± 10.4	Deficient (<10) 42 Insufficient (10–30) 47
Blair et al. [7] (2008)	USA	retrospective, multi-centered	HD (344)	37.1 ± 34.5	61.9 ± 16.3	21.0 ± 13.5	Deficiency (<40) 92.4
Porter et al. [8] (2013)	USA	retrospective	HD (96)	68.4 ± 55.2	52.5 ± 14.6	14.7 ± 6.0	Deficient (<15) 56 Insufficient (16–30) 44
Alwakeel et al. [14] (2014)	Saudi Arabia	cross-sectional	PD (27)	27.5 ± 18.5	46.0 ± 21.0	16.1 ± 8.2	Deficient (<15) 59.2 Insufficient (15–25) 29.6
Ewers et al. [16] (2008)	Denmark	cross-sectional	KT (173)	88.8(39.6–152.4)	53.4 ± 11.7	F 21.6 (15–31) M 18.2 (12–27)	Deficient (<15) 29.0 Insufficient (16–30) 51.0
Marcen et al. [17] (2009)	Spain	retrospective	KT (509)	113.0±76.0	45.4 ± 14.5	20.0 ± 10.6	Deficient (<16) 38.3 Insufficient (16–30) 46.9
Kulshrestha et al. [18] (2013)	USA	cross-sectional	KT (74)	51.2 (47.9–53.5)	46.0 ± 16.0	MS 20.5 ± 7.2 Without MS 24.8 ± 11.1	Deficient (<16) 29.7 Insufficient (16–30) 51.4
Beique et al. [19] (2013)	Canada	retrospective	KT (331)	80.4 (34.8–129.6)	51.0 (41.5-60.2)	31.3 (23.4–39.9)	Deficient (<30) 45.3
Clayton et al. [13] (2009)	Australia	cross-sectional	HD (120) PD (31)	29.5 (11.6–53.1) 20.6(10.5–43.8)	64.1(53.1–74.7) 68.6 (58.1–72.1)	20.0 (12.7–26.0) 13.6 (8.4–15.0)	HD deficient (<20) 49 HD insufficient (20–30) 33 PD deficient 77 PD insufficient 19
Iguacel et al. [11] (2010)	Spain	cross-sectional	OL-HDF (33) HD (61) PD (21)	27.5 (12.0–70.5)	60.0 ± 16.0	19 (13–27) 11 (6–16) 9 (6–12)	Deficient (5–15) 51.0 Insufficient (16–30) 42.0
Hanna et al. [10] (2014)	Australia	cross-sectional	HD (26) PD (30)	22 (2–166) 17 (1–70)	63.6 ± 15.1 56.9 ± 16.2	21.5 (4.1–50.4) 13.2 (5.0–33.2)	HD deficient (<10) 3.8 HD insufficient (10–20) 30.8 PD deficient 33.3 PD insufficient 43.3

Table 1. (Con) Summary of studies of prevalence of 25(OH)D deficiency in various renal replacement therapy modalities

Authors (year)	Countries	Study design	Population (n)	Duration of RRT (months)	Age (years)	[25(OH)D] (ng/mL)	Prevalence of low [25(OH)D] (ng/mL) %
Eyal et al. [15] (2013)	Israel	cross-sectional	HD (50)	90.4 ± 74.6	56.2 ± 15.4	30.3 ± 19.1 23.5 ± 9.9	HD deficient (<15) 10 HD insufficient (16–30) 52
			KT (103)				KT deficient 22.3 KT insufficient 52.4
The present study 44	Thailand	cross-sectional, retrospective,	OL-HDF (32)	72.6 ± 57.4	55.5 ± 16.8	17.7 ± 8.5	OL-HDF deficient (<15) 50 OL-HDF insufficient (15–30)
		single-center	PD (37)			10.5 ± 5.9	PD deficient 82 PD insufficient 18
			KT (42)			15.4 ± 6.1	KT deficient 55 KT insufficient 45

Data presented as mean ± SD, median (percentile 25th–75th) and [range]. F, female; M, male; OL-HDF, online-hemodiafiltration; PD, peritoneal dialysis; HD, hemodialysis; KT, kidney transplant recipient; MS, metabolic syndrome; RRT, renal replacement therapy

Table 2. Baseline characteristics of patients whose data were included in the study

Variable	OL-HDF (n = 32)	PD (n = 37)	KT (n = 42)	*P*
Demographic data				
Age (y)	54.3 ± 14.2	64.7 ± 19.5*	48.3 ± 11.7	**<0.001**
Male sex, n (%)	11 (34.4)	15 (40.5)	20 (47.6)	0.51
Body weight (kg)	52.0 (18)	53.3 (11)	60.3 (21)	0.32
Body mass index (kg/m^2)	20.5 (8)	21.0 (5)	22.3 (6)	0.47
RRT duration (years)	5.6 (6.7)	3.5 (2.9)*	4.7 (8.6)	**0.006**
Presence of diabetes, n (%)	12 (37.5)	18 (48.6)	7 (16.7)**	**0.009**
Medications				
RAS blockade (%)	40.6	48.6	26.2	0.11
Erythropoietin (units/kg)	209.8 ± 206.3	150.7 ± 133.3	73.2 ± 44.8	0.14
Cause of end stage renal disease				
Diabetic nephropathy	9 (28.1%)	17 (45.9%)	5 (11.9%)	**0.003**
Glomerulonephritis	6 (18.7%)	6 (16.2%)	18 (42.9%)	**0.01**
Obstruction	2 (6.3%)	2 (5.4%)	2 (4.8%)	0.96
Polycystic kidney disease	1 (3.1%)	1 (2.7%)	3 (7.1%)	0.58
Hypertension	10 (31.3%)	5 (13.5%)	1 (2.1%)	**0.002**
Unknown	4 (12.5%)	6 (16.2%)	13(31.0%)	0.11
Laboratory variables				
25(OH)D (ng/mL)	17.7 ± 8.5	10.5 ± 5.9*	15.4 ± 6.1	**<0.001**
Hemoglobin (g/dL)	10.9 (1.2)	11.0 (1.6)	11.9 (2.4)**	**0.003**
Blood urea nitrogen (mg/dL)	72.6 ± 24.0	52.7 ± 22.7	24.5 ± 17.5**	**<0.001**
Creatinine (mg/dL)	10.3 (3.2)	8.0 (6.3)	1.2 (0.9)**	**<0.001**
Uric acid (mg/dL)	7.6 ± 1.5$^{\#}$	5.9 ± 1.3	6.9 ± 2.3	**0.001**
Bicarbonate (mEq/L)	24.1 ± 2.3	26.2 ± 3.0*	23.7 ± 3.4	**0.001**
Corrected calcium (mg/dL)	9.5 (1.2)	9.5 (0.9)	9.6 (1.0)	0.68
Phosphate (mg/dL)	4.9 (1.4)	4.2 (1.4)	3.3 (0.8)**	**<0.001**
Total cholesterol (mg/dL)	157.9 ± 30.9$^{\#\#}$	175.3 ± 45.5	195.4 ± 43.5	**0.001**
Triglyceride (mg/dL)	98 (71.5)	127.0 (149)	117.5 (66.3)	0.21
Low density lipoprotein (mg/dL)	88.0 (30.3)	84 (31.5)	112.5 (55)	**0.05**
High density lipoprotein (mg/dL)	48.7 ± 14.5	42.9 ± 18.8	63.8 ± 21.7**	**<0.001**
Intact parathyroid hormone (pg/mL)	534.4 (496.8)	288.8 (339.0)	106.2 (231.4)**	**0.001**
Albumin (g/dL)	4.1 (0.8)	3.6 (0.8)*	4.2 (0.5)	**<0.001**
Kt/V	2.4 ± 0.4	2.2 ± 0.5	NA	0.07
nPNA (g of N/kg/day)	1.1 (0.4)	1.0 (0.3)	1.0 (0.4)	0.10

OL-HDF, online-hemodiafiltration; PD, peritoneal dialysis; KT, kidney transplant recipient; RAS, renin–angiotensin system; RRT, renal replacement therapy; NA, not applicable; nPNA, normalized protein nitrogen appearance; 25(OH)D, 25-hydroxyvitamin D (calcifediol)

Data are presented as mean ± SD and median (interquartile range, IQR).

*$P < 0.05$ in PD group when compared with OL-HDF and KT. **$P < 0.05$ in KT group when compared with OL-HDF and PD. $^{\#}P < 0.05$ in OL-HDF group when compared with PD. $^{\#\#}P < 0.05$ in OL-HDF group when compared with KT.

(81% deficient, 19% insufficient), 100% of KT recipients (55% deficient, 45% insufficient), and 94% of patients receiving OL-HDF (50% deficient, 44% insufficient). Only 2% of the patients had normal serum [25(OH)D] (30–80 ng/mL) and were in OL-HDF group.

Patients in the PD group had a significantly lower level of serum 25(OH)D than those in the OL-HDF and KT groups. All patients with severe vitamin D deficiency, that is, serum [25(OH)D] <5 ng/mL, were maintained on PD. Patients receiving PD were significantly older and had less dialysis vintage (years of treatment) than patients in the OL-HDF and KT groups. In the PD group, there were no significant differences in age, sex, history of diabetes, BMI, adequacy of dialysis, or serum albumin, calcium, or

phosphate between those with CAPD and APD. Patients with APD tended to have a lower mean serum [25(OH)D] than those with CAPD, but the difference was not quite significant.

Vitamin D-deficient (<15 ng/mL) OL-HDF patients had significantly lower vascular access flow, lower hemoglobin levels, and significantly higher BMI than OL-HDF patients with 25(OH)D ≥15 ng/mL (**Table 3**).

DDKT recipients had significantly lower mean [25(OH)D] than patients with LRKT (**Table 4**).

Notably, LRKT recipients had significantly higher serum albumin and lower 24-hour urine protein loss than those in the DDKT group. There was no significant difference in age, renal function, BMI, immunosuppressive regimen, or prednisolone dose between KT recipient subgroups.

Determinants of 25(OH)D deficiency among patients receiving RRT

There were no significant differences in serum [25(OH)D] between patients of either sex, with or without diabetes, or high or low BMI (data not shown). Multiple logistic regression analysis showed treatment with renin angiotensin system (RAS) blockade, serum triglyceride, and iPTH were significantly associated with 25(OH)D deficiency in patients receiving RRT, and that serum uric acid and phosphate had a significant inverse association with vitamin D deficiency (**Table 5**).

Table 3. Laboratory variables in patients receiving dialysis

Variable	OL-HDF			PD		
	25(OH)D <15 ng/mL[a] (n = 16)	25(OH)D ≥15 ng/mL[b] (n = 16)	*P*	APD (n = 24)	CAPD (n = 13)	*P*
Demographic data						
Age (years)	51.4 ± 14.3	57.1 ± 13.9	0.26	64.3 ± 20.0	65.5 ± 19.3	0.87
Male sex, n (%)	4 (25.0)	7 (43.8)	0.26	10 (41.7)	5 (38.5)	0.85
Dialysis duration (years)	7.6 ± 5.9	6.4 ± 4.8	0.54	4.3 ± 2.2	3.6 ± 1.7	0.32
Diabetes, n (%)	7 (43.8)	5 (31.3)	0.46	13 (54.2)	5 (38.5)	0.36
Treatment with RAS blockade,n (%)	9 (56.3)	4 (25.0)	**0.07**	13 (54.2)	5 (38.5)	0.36
History of peritonitis (%)	NA	NA	NA	11 (45.8)	1 (7.7)	**0.02**
Vitamin D status and adequacy of dialysis						
25(OH)D (ng/mL)	11.4 ± 2.4	23.9 ± 7.7	**0.001**	9.3 ± 5.1	12.7 ± 6.7	0.09
Kt/V*	2.4 ± 0.5	2.3 ± 0.3	0.73	2.2 ± 0.5	2.1 ± 0.4	0.41
URR (%)	84.6 ± 6.6	85.8 ± 3.2	0.52	NA	NA	NA
Access blood flow (mL/min)	832.9 ± 364.9	1,238.9 ± 384.9	**0.008**	NA	NA	NA
Weekly CCl (mL/min)	NA	NA	NA	61.3 ± 32.3	64.1 ± 20.1	0.78
Nutritional variable						
Body mass index (kg/m^2)	25.4 ± 7.7	20.3 ± 2.9	**0.02**	21.8 ± 3.6	22.1 ± 3.7	0.81
nPNA (g of N/kg/day)	1.1 ± 0.3	1.2 ± 0.5	0.34	1.05 ± 0.3	1.07 ± 0.3	0.84
Serum albumin (g/dL)	4.0 ± 0.4	4.1 ± 0.5	0.45	3.3 ± 0.5	3.6 ± 0.7	0.21
Protein loss via dialysate (g/day)	NA	NA	NA	4.7 ± 3.2	5.1 ± 1.6	0.66
Bone metabolism and laboratory variable						
Hemoglobin (g/dL)	10.2 ± 1.1	11.3 ± 1.3	**0.02**	11.2 ± 1.3	10.7 ± 2.1	0.38
Uric acid (mg/dL)	7.4 ± 1.4	7.7 ± 1.6	0.64	6.0 ± 1.6	5.9 ± 0.7	0.72
Corrected calcium (mg/dL)	9.5 ± 0.9	9.5 ± 0.7	0.93	9.6 ± 0.9	9.5 ± 0.8	0.76
Phosphate (mg/dL)	4.7 ± 1.5	5.0 ± 1.1	0.53	4.4 ± 1.5	4.6 ± 1.3	0.68
iPTH (pg/mL)	743.8 ± 505.0	454.9 ± 248.1	0.09	518.5 ± 601.9	521.9 ± 615.2	0.98
hs-CRP (mg/L)	6.6 ± 9.8	4.9 ± 4.5	0.55	6.3 ± 6.8	6.7 ± 7.8	0.88

OL-HDF, online-hemodiafiltration; PD, peritoneal dialysis; *weekly Kt/V for patients receiving PD; 25(OH)D, 25-hydroxyvitamin D (calcifediol); APD, ambulatory PD; CAPD, continuous ambulatory PD; RAS, renin–angiotensin system; CCl, Creatinine clearance; hs-CRP, high sensitive C-reactive protein; NA, not applicable; iPTH, intact parathyroid hormone; RAS, renin–angiotensin system; URR, urea reduction ratio; nPNA, normalized protein nitrogen; [a]Deficiency; [b]Insufficiency

Table 4. Laboratory variables in kidney transplant (KT) recipients

Variable	KT deceased donor (n = 23)	KT living, related donor (n = 19)	*P*
Demographic data			
25(OH)D (ng/mL)	13.7 ± 6.0	17.5 ± 5.7	**0.046**
Age (years)	48.5 ± 10.5	48.1 ± 13.3	0.91
Male sex, n (%)	12 (52.2)	8 (42.1)	0.52
Post transplantation time (years)	7.6 ± 5.7	6.5 ± 5.4	0.51
Treatment with RAS blockade, n (%)	7 (30.4)	4 (21.1)	0.49
Diabetes, n (%)	5 (21.7)	2 (10.5)	0.33
Immunosuppressive regimen			
Prednisolone use, n (%)	12 (52.2)	14 (73.7)	0.15
Tacrolimus-based, n (%)	8 (34.8)	9 (47.4)	0.41
Renal functions and urine collection			
Blood urea nitrogen (mg/dL)	27.4 ± 15.3	21.1 ± 19.6	0.25
Creatinine (mg/dL)	1.9 ± 2.2	1.5 ± 1.5	0.45
24-Hour urine protein (g/day)	1.7 ± 2.8	0.4 ± 0.3	**0.045**
Nutritional variables and other laboratory findings			
Body mass index (kg/m^2)	23.1 ± 4.2	23.2 ± 4.4	0.97
Albumin (g/dL)	3.9 ± 0.5	4.3 ± 0.4	**0.02**
nPNA (g of N/kg/day)	1.1 ± 0.3	0.9 ± 0.2	**0.049**
Hemoglobin (g/dL)	11.8 ± 1.7	12.1 ± 1.6	0.55
Fasting blood sugar (mg/dL)	93.9 ± 18.5	109.9 ± 57.3	0.21
Uric acid (mg/dL)	6.9 ± 2.5	6.8 ± 2.1	0.79
Corrected calcium (mg/dL)	9.7 ± 0.8	9.6 ± 0.6	0.58
Phosphate (mg/dL)	3.3 ± 1.0	3.4 ± 0.7	0.77
iPTH (pg/mL)	267.0 ± 297.3	144.8 ± 145.3	0.13

25(OH)D, 25-hydroxyvitamin D (calcifediol); nPNA, normalized protein nitrogen; iPTH, intact parathyroid hormone

Table 5. Multiple logistic regression analysis of 25-hydroxyvitamin D (calcifediol) deficiency (<15 ng/mL) in 111 patients with renal replacement therapy

Determinants	Unadjusted OR	95% CI	*P*	Adjusted OR	95% CI	*P*
Treatment with RAS blockade	5.15	2.01, 13.16	**0.001**	7.45	2.17, 25.62	**0.001**
Triglyceride (mg/dL)*	1.08	1.02, 1.14	**0.009**	1.08	1.01, 1.16	**0.03**
Uric acid (g/dL)	0.75	0.59, 0.94	**0.01**	0.72	0.52, 0.99	**0.04**
iPTH (pg/mL)**	1.01	1.00, 1.02	**0.04**	1.02	1.00, 1.04	**0.02**
Phosphate (mg/dL)	0.95	0.71, 1.26	0.72	0.57	0.36, 0.90	**0.02**
Calcium (mg/dL)	0.89	0.55, 1.43	0.62	0.61	0.30, 1.23	0.17
Albumin (g/dL)[#]	0.94	0.88, 1.01	0.08	0.93	0.85, 1.02	0.11
Female gender	1.76	0.81, 3.84	0.16	2.42	0.86, 6.82	0.10

OR, odds ratio; CI, confidence interval, RAS, renin–angiotensin system; *OR per 10 mg/dL increase in serum triglyceride, **OR per 10 pg/mL increase in serum iPTH, [#]OR per 0.1 g/dL increase in serum albumin.

Serum calcium, albumin, and female sex were not found significantly associated with serum 25(OH)D deficiency by multivariate analysis. Among patients receiving dialysis, treatment with RAS blockade and serum triglyceride level were significantly associated with 25(OH)D deficiency. In KT recipients, treatment with RAS blockade and older age were significantly associated with 25(OH)D deficiency after adjustment for confounding factors (data not shown).

Discussion

The present study demonstrates that low vitamin D status (25(OH)D insufficiency or deficiency) was observed in 100% of patients receiving PD or with KT, and 94% of patients receiving OL-HDF. Patients receiving PD had the lowest [25(OH)D] among patients with the 3 different types of RRT, while the levels were comparable between the OL-HDF and KT group. **Table 1** details the prevalence of 25(OH)D insufficiency or deficiency found in previous studies. The high prevalence of 25(OH)D insufficiency and deficiency found by the present study was consistent with recent studies [9, 10, 14].

In the present study, patients receiving PD were the oldest and had significantly lower serum albumin levels than OL-HDF and KT recipient patients (**Table 2**). Both of these factors might be associated with the low [25(OH)D]. The aging process can be associated with a decreased ability to produce vitamin D cutaneously because of the reduced amount of its precursor, 7-dehydrocholesterol, and atrophic skin changes compared with younger people despite a similar time of exposure to ultraviolet light [28]. Furthermore, one study found that total sun exposure time and dietary vitamin D intake had no significant association with serum [25(OH)D] in patients receiving PD [10]. Another explanation for the low [25(OH)D] in patients receiving PD is that PD causes continuous loss of vitamin D and vitamin D binding protein together with albumin through the peritoneal effluent [29, 30]. Pediatric patients receiving continuous cycling PD had a lower mean serum [25(OH)D] than those receiving nightly intermittent PD [12]. However, we did not find any significant differences in serum [25(OH)D], serum albumin, and the amount of protein loss via dialysate between patients receiving APD or CAPD.

As seen in **Table 3**, OL-HDF patients with vitamin D deficiency had significantly lower vascular access flow than OL-HDF patients without deficiency. Vitamin D deficiency can lead to decreased endothelial function as assessed by flow-mediated vasodilation, and increased arterial stiffness as assessed by pulse wave velocity in patients with end stage renal disease [31]. In the present study, OL-HDF patients with 25(OH)D deficiency had higher BMI, but lower hemoglobin levels, than patients with insufficient 25(OH)D (**Table 3**). Our findings were consistent with those of Del Valle et al. [9] who found that BMI had an inverse correlation with serum 25(OH)D level, and Kiss et al. [32] showed a significant positive correlation of serum 25(OH)D with hemoglobin level and erythropoietin responsiveness in patients on maintenance HD. This suggests that 25(OH)D exerts its pleiotropic effects by direct stimulation of erythroid precursor cells [33].

Calcineurin inhibitors can suppress vitamin D receptor expression, and corticosteroids can enhance catabolism of vitamin D [34]. Nevertheless, no significant differences for immunosuppressive regimen and corticosteroid dose were observed between DDKT recipients who had significantly lower serum [25(OH)D] than LRKT recipients (**Table 4**). DDKT recipients had significantly higher proteinuria than LRKT recipients. Lee et al. found LRKT recipients with 25(OH)D insufficiency had significantly higher proteinuria than a group of control recipients with sufficient levels of 25(OH)D (>30 ng/mL) [35].

Earlier studies found that factors associated with 25(OH)D deficiency in patients receiving maintenance dialysis were female sex, diabetes mellitus, BMI, serum albumin, presence of residual renal function, and average sun exposure time [9-13]. Among post KT recipients, serum 25(OH)D concentration positively correlated with age, type of immuno-suppressive agent, use of corticosteroid, time from transplantation, and the presence of metabolic syndrome [15, 18], while BMI and treatment by RAS blockade were inversely correlated with 25(OH)D deficiency [16, 17]. In the present study, multivariate regression analysis (**Table 5**) found treatment with RAS blockade and elevated serum iPTH was significantly associated with 25(OH)D deficiency. Meta-analysis and epidemiological studies found that treatment by RAS blockade was common in hypertensive patients with CKD, and high blood pressure has an inverse association with serum [25(OH)D] [36, 37]. However, the mechanism is not well understood. Evidence for a causal relationship is still lacking, and this issue warrants further investigation, particularly in patients receiving RRT. We found no association between age, female sex, diabetes, BMI, or serum albumin, and 25(OH)D deficiency (**Table 5**). The present study showed that serum triglyceride was significantly associated with vitamin D deficiency. Indeed, serum triglyceride was previously reported as having an inverse relationship with vitamin D deficiency in a cohort of patients with CKD predialysis [38], but no significant association was found in KT

recipients [18]. 25(OH)D deficiency may result in decreased hepatocellular calcium levels, which may in turn stimulate hepatic triglyceride formation [39].

The present study had some limitations. The number of patients in the present study was small. Because we included data only from patients with preexisting serum [25(OH)D] measurements, there might be a selection bias. In an attempt to circumvent this problem, we adjusted for confounding factors in the statistical analysis. The factors associated with [25(OH)D] do not provide proof of a causal relationship. There was no consideration of the effect of [25(OH)D] fluctuation because of dietary vitamin D supplementation in the present study, because the patients who previously consumed supplemental ergocalciferol or cholecalciferol were not included. Further studies are required to determine whether native vitamin D supplementation will improve clinical or laboratory variables in patients receiving RRT.

In conclusion, the present study emphasizes that the prevalence of vitamin D deficiency and insufficiency is high among patients receiving RRT, and modality of RRT may be a factor related to vitamin D deficiency.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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