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Significance of residual renal function for phosphate control in chronic hemodialysis patients

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Abstract

Background: The aim of this study was to compare mineral metabolism between anuric and nonanuric chronic hemodialysis patients, and determine the differences in phosphate control between the two groups.

Methods: A total of 77 chronic hemodialysis patients were enrolled in this cross-sectional study from January 2012 to February 2012. Patient demographics, laboratory findings, medication histories, and vascular calcification scores were collected. We divided the patients into anuric and nonanuric groups according to the residual renal function and then compared their clinical features. Multivariate binary regression analysis was used in each group to determine the independent factors related to phosphate control.

Results: The mean patient age was 59.27 ± 13.95 years, and 57.1% of patients were anuric. In anuric patients, dialysis vintage was significantly longer, but the mean Kt/V was not different between groups. Serum phosphate, fibroblast growth factor (FGF)-23, and Ca/P products were significantly higher, and $1,25(OH)_2D_3$ levels were significantly lower in the anuric patients, although the intact parathyroid hormone and 25(OH)D levels were not different. In anuric patients, LnFGF-23 [hazard ratio (HR) 2.894, 95% confidence interval (CI) 1.294–6.474, $P=0.010$] was an independent factor predictive of phosphate control. However, in the nonanuric patients, glomerular filtration rate (HR 0.409, 95% CI 0.169–0.989, $P=0.047$) and blood urea nitrogen (HR 1.090, 95% CI 1.014–1.172, $P=0.019$) were independent factors predictive of phosphate control.

Conclusion: In chronic hemodialysis patients, preservation of residual renal function is a significant determinant of phosphate control, and the factors associated with phosphate control is different depending on the residual renal function status. In the anuric patients, FGF-23 is most significantly associated with phosphate control; however, glomerular filtration rate and blood urea nitrogen are more important than FGF-23 in the nonanuric HD patients.

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Introduction

Residual renal function (RRF) is an important determinant of mortality and morbidity in chronic dialysis patients. In previous studies, the degree of RRF was found to be inversely associated with the severity of left ventricular hypertrophy and cardiovascular death in peritoneal dialysis patients [1,2]. Preserved RRF was also observed to be associated with better all-cause and cardiac-specific mortality in hemodialysis (HD) patients [3,4]. These associations may be related to the better clearance of mid to large molecular uremic toxin and fluid removal from the residual kidney in nonanuric dialysis patients [5,6].

Phosphate, which is excreted through urine, is the key molecule in chronic kidney disease-mineral and bone disorder (CKD-MBD). Under normal physiologic conditions, phosphate removal is determined mainly by the expression of type II Na–Pi cotransporters at the tubular epithelium [7], which are controlled by dietary phosphate, parathyroid hormone (PTH), vitamin D, and fibroblast growth factor-23 (FGF-23) [8,9]. In chronic dialysis patients with RRF, phosphate can be excreted through the remnant nephron; however, in anuric dialysis patients, serum phosphate cannot be excreted through urine. Therefore, phosphate control may differ depending on the RRF status.

In this study, we aimed to compare mineral metabolism between anuric and nonanuric chronic HD patients and determine the differences in phosphate control between these groups according to RRF.

Methods

Participants

From January 2012 to February 2012, a total of 77 HD patients from our dialysis unit were enrolled in this study. All patients were older than 18 years and undergoing maintenance HD therapy for end-stage renal disease for more than 3 months. The participants were dialyzed thrice weekly for more than 4 hours per session, using low-flux membranes. The standard dialysate calcium concentration was 3.5 mEq/L. Exclusion criteria included severe malnutrition, acute infection, hepatic dysfunction, and malignancy. Approval of the local ethics committee was obtained for this study, and all patients provided written informed consent.

Data collection

Demographics and medical histories were reviewed; dialysis treatment parameters such as dialysis vintage, blood flow rate, and single-pool Kt/V were assessed; and nutritional markers, such as normalized protein nitrogen appearance (nPNA), subjective global assessment (SGA), total protein, albumin, and total cholesterol levels were checked. Biochemical CKD-MBD factors and associated medication histories during the study period were collected. All the predialysis blood samples were obtained for routine laboratory assessment by standard techniques, and a part of these samples was stored at -80°C for performing the enzyme-linked immunosorbent assay (ELISA) study in all patients. Analysis of serum calcium was performed by the ortho-cresolphthalein complexone method using a Roche/Hitachi Modular-DP analyzer (Roche Diagnostics, Basel, Switzerland); calcium levels were corrected for serum albumin. Analysis of serum phosphate was performed by the phosphomolybdate reduction method using a Roche/Hitachi Modular-DP analyzer (Roche Diagnostics). The serum level of intact PTH (iPTH) was assessed by a total iPTH immunoradiometric assay, which quantifies both PTH(1–84) and the N-truncated PTH fragments. Serum 25(OH)D and 1,25 $(OH)_2D_3$ levels were measured using a radio immunoassay. Serum FGF-23 and serum fetuin A levels were measured using an ELISA kit (ELISA, Immutopics, San Clemente, CA, USA—for FGF-23; ELISA, R&D Systems, Minneapolis, MN, USA—for feutin A), according to the manufacturer's protocol.

Calculations and definitions

We defined anuria as a 24-hour urine output of < 100 mL, and the glomerular filtration rate (eGFR) of the anuric patients was estimated to be 0.00 mL/minute/1.73 m^2. For the nonanuric patients, GFR was estimated by the numerical averages of the 24-hour creatinine clearance and urea nitrogen clearance. A 24-hour urine collection was made after the longest interdialysis period. A cardiovascular event was defined as myocardial infarction, stroke, or transient ischemic attack. Single-pool Kt/V (spKt/V) was calculated using the natural logarithm formula [10], and the nPNA was calculated according to the method of Bergström et al [11]. The optimal phosphate level was defined as the phosphate level between 2.5 mg/dL and 4.5 mg/dL, which is considered a normal value in our clinic. All medications were prescribed according to the 2009 Kidney Disease: Improving Global Outcome CKD-MBD treatment guidelines.

Aortic arch calcifications were calculated based on posterior–anterior plain chest X-rays, using Ogawa et al's method [12], by a physician who was independent of this study. The intraobserver variability of this method was 5.3%.

Statistical analysis

Data were analyzed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). For continuous variables, the mean $\pm$ standard deviation was used for normally distributed data; otherwise, the median was shown. Differences between the two groups were assessed using a Student t test or Chi-square test, as appropriate. Pearson or Spearman correlation coefficients were used to test the correlation between eGFR and other variables. To evaluate the influence of parameters on the control of optimal phosphate levels, nonparametric variables were Ln-transformed to achieve normality; after transformation of the variables, we performed binary logistic regression analysis. A P value of < 0.05 was considered statistically significant.

Table 1. Causes of end-stage renal disease

Diagnosis	%
Diabetes	53.25
Glomerulonephritis	20.78
Hypertension	14.28
ADPKD	6.49
Neurogenic bladder	3.89
Unknown	1.29

Data are presented as %.
ADPKD, autosomal dominant polycystic kidney disease.

Results

Patent characteristics according to RRF

A total of 77 patients were enrolled in this study. The mean patient age was 59.27 ± 13.95 years, and 59.7% of patients were male. Diabetes was the most common cause of end-stage renal disease, the various causes of which are listed in Table 1.

In our study, 57.1% ($N=44$) of the patients were anuric. Dialysis vintage was significantly longer in the anuric patients than in the nonanuric patients. The spKt/V was not significantly different, and a minimally adequate dialysis dose (spKt/V > 1.2) was equally achieved in both groups. Nutritional factors, including nPNA and SGA, were not significantly different. Regarding the biochemical CKD-MBD factors, serum phosphate, Ca/P product, and FGF-23 levels were significantly lower and $1,25(OH)_2D_3$ levels were significantly higher in the nonanuric patients, although the frequency of prescribed medications for phosphate control was not significantly different between groups. However, serum iPTH and 25(OH)D levels were not different, according to the RRF status. For the factors related to vascular calcification, serum fetuin A levels were similar, and the frequency of aortic arch calcification or the aortic arch calcification score was not significantly different between groups (Table 2).

With the unadjusted analysis, serum phosphate ($r=-0.16$, $P < 0.001$) and FGF-23 ($r=-0.18$, $P=0.001$) levels showed a negative correlation with eGFR, whereas $1,25(OH)_2D_3$ ($r=0.79$, $P < 0.001$) showed a positive correlation. However, iPTH, alkaline phosphatase, and 25(OH)D levels did not show any correlation with eGFR.

Factors associated with phosphate control in all patients

We further divided the patients into two groups according to the achievement of optimal phosphate control. Of the patients, 44.1% ($N=34$) achieved optimal phosphate control, and in none of them the phosphate level was lower than 2.5 mg/dL. The mean serum phosphate level was 3.57 ± 0.60 mg/dL in the optimal phosphate control group and 5.94 ± 1.12 mg/dL in the poor phosphate control group. In the optimal phosphate control group, serum FGF-23 (335.86 ± 390.33 pg/mL vs. 3,313.83 ± 5.36 pg/mL, $P=0.003$), blood urea nitrogen (BUN; 50.39 ± 14.60 mg/dL vs. 67.95 ± 17.47 mg/dL, $P<0.001$), creatinine (7.36 ± 2.37 mg/dL vs. 10.01 ± 2.51 mg/dL, $P<0.001$) and Ca × P levels

Table 2. Baseline characteristics according to the urine output status

Variables	Nonanuric patients	Anuric patients	*P*
N	33	44	
Age (y)	56.75 ± 14.24	62.64 ± 13.00	0.986
Male	48	61	0.737
DM	18.2	33.8	0.147
HT	75.8	61.4	0.182
Hx of CVE	37.0	38.1	0.845
GFR (mL/min/1.73 m^2)	6.40 ± 2.65	0.00 ± 0.00	<0.001
Dialysis factor			
Dialysis vintage (mo)	20.73 ± 16.87	41.73 ± 25.94	0.031
BFR (mL/min)	260.00 ± 15.61	265.45 ± 21.93	0.228
Kt/V	1.55 ± 0.37	1.48 ± 0.21	0.274
Nutrition factors			
nPNA (g/kg/d)	1.02 ± 0.26	1.10 ± 0.27	0.865
SGA	6.70 ± 0.59	6.70 ± 0.83	0.728
Total protein (g/dL)	6.75 ± 0.52	6.97 ± 0.56	0.473
Albumin (g/dL)	3.96 ± 0.48	4.14 ± 0.43	0.398
Total cholesterol (mg/dL)	147.91 ± 29.73	150.09 ± 32.63	0.385
BUN (mg/dL)	54.67 ± 19.22	64.34 ± 16.79	0.867
Creatinine (mg/dL)	7.92 ± 2.78	9.53 ± 2.59	0.479
Hb (g/dL)	10.29 ± 1.03	10.72 ± 1.32	0.449
Biochemical CKD-MBD factors			
Corrected calcium (mg/dL)	9.09 ± 0.73	9.18 ± 0.76	0.860
Phosphate (mg/dL)	4.32 ± 1.0	5.32 ± 1.66	0.017
Ca × P (mg^2/dL^2)	38.96 ± 9.75	49.53 ± 16.06	0.025
ALP (IU/L)	73.15 ± 30.37	92.48 ± 52.05	0.068
FGF-23 (pg/mL)	856.25 ± 2,297.58	2,849.09 ± 5,141.40	0.002
iPTH (pg/mL)	135.51 ± 105.62	156.93 ± 140.24	0.238
25(OH)D (ng/mL)	11.45 ± 5.80	11.05 ± 3.96	0.739
$1,25(OH)_2D_3$ (pg/mL)	13.03 ± 7.70	9.67 ± 3.46	0.020
Optimal phosphate group	59.4	31.8	0.014
Medications for the phosphate control			
Calcium acetate	24.7	32.5	0.737
Sevelamer	2.6	9.1	0.183
Lanthanum	0	1.3	0.383
Vitamin D	5.2	6.5	0.918
Vascular calcification			
Presence of AoAC	17.3	25.3	0.758
AoACS (%)	12.69 ± 19.85	13.95 ± 25.14	0.589
Fetuin A (μg/mL)	412.12 ± 93.99	429.09 ± 130.59	0.770

Data are presented as % or mean ± SD, unless otherwise indicated.

ALP, alkaline phosphatase; AoAC, aortic arch calcification; AoACS, aortic arch calcification score; BFR, blood flow rate; BUN, blood urea nitrogen; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; Hb, hemoglobin; HT, hypertension; Hx of CVE, history of cardiovascular event; iPTH, intact parathyroid hormone; nPNA, normalized protein nitrogen appearance; SD, standard deviation; SGA, subjective global assessment.

(32.59 ± 5.72 mg^2/dL^2 vs. 54.77 ± 11.78 mg^2/dL^2, $P=0.01$) were significantly lower and eGFR (4.32 ± 4.26 mL/minute/1.73 m^2 vs. 1.49 ± 2.42 mL/minute/1.73 m^2, $P<0.001$) and $1,25(OH)_2D_3$ level (13.76 ± 7.55 pg/mL vs. 9.32 ± 3.64 pg/mL, $P=0.003$) were statistically higher than in the poor phosphate control group. Uni- and multivariate regression analyses were performed after adjusting for these factors.

In the univariate analysis, LnFGF-23, $1,25(OH)_2D_3$, GFR, BUN, creatinine, and age were significant factors; however, in the multivariate regression model, LnFGF-23, $1,25(OH)_2D_3$,

Table 3. Multivariate analysis that relates to predialysis serum phosphate level, in all patients*

Variables	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
LnFGF-23 (pg/mL)	2.371	1.495–3.761	<0.001	1.991	1.147–3.458	0.014
$1,25(OH)_2D_3$ (pg/mL)	0.824	0.709–0.957	0.004	0.777	0.641–0.942	0.010
GFR (mL/min/1.73 m^2)	0.779	0.668–0.909	0.001	0.776	0.620–0.970	<0.001
BUN (mg/dL)	1.075	1.034–1.117	<0.001			
Cr (mg/dL)	1.542	1.211–1.963	<0.001			
Age (y)	0.951	0.914–0.989	0.012			

* Adjusted age, sex, LnFGF-23, $1,25(OH)_2D_3$, GFR, BUN, and Cr.
BUN, blood urea nitrogen; CI, confidence interval; Cr, creatinine; GFR, glomerular filtration rate; HR, hazard ratio; LnFGF-23, log-transformed fibroblast growth factor-23.

Table 4. Comparisons of phosphate control according to the residual renal function in chronic hemodialysis patients

Variables	Nonanuric patients			Anuric patients		
	Optimal P control	Poor P control	*P*	Optimal P control	Poor P control	*P*
Number	20	13		14	30	
Age (y)	66.37 ± 10.54	58.23 ± 15.03	0.081	61.25 ± 7.51	54.74 ± 15.98	0.078
Male	57.9	53.8	0.821	75.0	54.8	0.306
DM	47.4	38.5	0.618	75.0	54.8	0.306
HT	73.7	76.9	0.835	91.7	51.6	0.032
Hx of CVE	41.7	36.7	0.763	41.7	36.7	0.763
GFR (mL/min/1.73 m^2)	7.28 ± 2.89	5.20 ± 1.84	0.030	0	0	–
Dialysis factor						
Dialysis vintage (mo)	22.58 ± 18.26	16.31 ± 13.80	0.303	45.92 ± 24.24	41.35 ± 26.29	0.605
BFR (mL/min)	257.37 ± 9.91	260.76 ± 18.91	0.560	265.00 ± 23.16	266.13 ± 22.01	0.886
Kt/V	1.58 ± 0.42	1.52 ± 0.30	0.648	1.46 ± 0.21	1.50 ± 0.21	0.517
Nutrition factors						
nPNA (g/kg/d)	1.02 ± 0.31	1.02 ± 0.19	0.999	1.03 ± 0.19	1.13 ± 0.29	0.246
SGA score	6.74 ± 0.56	6.64 ± 0.67	0.664	6.42 ± 1.16	6.81 ± 0.65	0.171
Total protein (g/dL)	6.64 ± 0.41	6.90 ± 0.63	0.169	7.06 ± 0.64	6.94 ± 0.54	0.510
Albumin (g/dL)	3.99 ± 0.39	3.92 ± 0.60	0.071	4.01 ± 0.32	4.18 ± 0.46	0.246
Total cholesterol (mg/dL)	145.32 ± 30.49	151.69 ± 29.36	0.560	147.33 ± 23.18	151.16 ± 35.90	0.735
BUN (mg/dL)	46.68 ± 14.89	67.27 ± 19.16	0.002	55.67 ± 14.84	68.10 ± 16.54	0.028
Creatinine (mg/dL)	6.73 ± 2.35	9.47 ± 2.63	0.004	8.39 ± 2.14	10.09 ± 2.58	0.048
Hb (g/dL)	10.37 ± 1.14	10.16 ± 0.92	0.581	10.47 ± 1.52	10.82 ± 1.27	0.456
Biochemical CKD-MBD factors						
Corrected calcium (mg/dL)	9.48 ± 0.66	9.51 ± 0.73	0.905	9.63 ± 0.72	9.42 ± 0.64	0.364
Phosphate (mg/dL)	3.59 ± 0.58	5.35 ± 0.60	<0.001	3.43 ± 0.56	6.13 ± 1.24	<0.001
Ca × P (mg^2/dL^2)	32.52 ± 5.46	48.37 ± 6.24	<0.001	31.78 ± 6.29	56.39 ± 13.11	<0.001
ALP (IU/L)	79.05 ± 27.58	67.77 ± 32.93	0.302	105.50 ± 54.65	87.10 ± 51.83	0.310
FGF-23 (pg/mL)	314.23 ± 456.39	658.31 ± 375.96	0.045	372.12 ± 304.20	3919.32 ± 5846.95	0.003
LnFGF-23 (pg/mL)	4.92 ± 1.33	6.21 ± 0.92	0.009	5.50 ± 1.12	7.09 ± 1.71	0.007
iPTH (pg/mL)	163.75 ± 115.07	101.92 ± 81.05	0.105	117.19 ± 101.73	167.61 ± 151.45	0.295
$1,25(OH)_2D_3$ (ng/mL)	15.27 ± 8.71	10.48 ± 5.08	0.100	11.19 ± 4.21	8.76 ± 2.65	0.047
Medications for the phosphate control						
Calcium acetate	63.2	53.8		58.3	64.5	
Average dose (mg/d)	597.89 ± 542.95	1301.67 ± 1625.64	0.598	650.83 ± 769.37	1088.67 ± 1082.94	0.210
Sevelamer	0 ± 0	15.4		0	22.6	
Average dose (mg/d)	0	369.23 ± 901.28	0.157	0 ± 0	541.94 ± 1020.06,	0.006
Lanthanum	0	0		0	3.2	
Average dose (mg/d)	0 ± 0	0 ± 0		0 ± 0	48.39 ± 269.41	0.540
Calcitriol	21.1	0		8.3	12.9	
Average dose (mcg/d)	0.05 ± 0.13	0 ± 0	0.128	0.02 ± 0.07	0.02 ± 0.06	0.854
Vascular calcification						
Presence of AoAC	47.4	30.8	0.348	41.7	45.2	0.836
AoACS score	15.78 ± 22.76	8.17 ± 14.29	0.294	9.37 ± 13.19	15.72 ± 28.45	0.464
Fetuin A (μg/mL)	381.68 ± 93.15	459.89 ± 81.49	0.030	409.89 ± 95.03	439.27 ± 142.92	0.551

Data are presented as % or mean ± SD.
ALP, alkaline phosphatase; AoAC, aortic arch calcification; AoACS, aortic arch calcification score; BFR, blood flow rate; BUN, blood urea nitrogen; CKD-MBD, chronic kidney disease-mineral and bone disorder; DM, diabetes mellitus; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; Hb, hemoglobin; HT, hypertension; Hx of CVE, history of cardiovascular event; iPTH, intact parathyroid hormone; nPNA, normalized protein nitrogen appearance; SD, standard deviation; SGA, subjective global assessment.

and GFR were independent factors predictive of optimal phosphate control (Table 3).

Factors associated with phosphate control in nonanuric patients

Among the 33 nonanuric patients, 59.4% ($N=20$) achieved optimal phosphate control, and the use of phosphate-binding agents in this group was not significantly different from that in the poor phosphate control group (63.2% vs. 69.2%, $P=0.598$). Other nonanuric patient characteristics according to the phosphate control are presented in Table 4.

In the univariate analysis, LnFGF-23, BUN, creatinine level, and GFR were statistically significant; however, in the multivariate analysis, GFR [hazard ratio (HR) 0.409, 95% confidence interval (CI) 0.169–0.989, $P=0.047$] and BUN (HR 1.090, 95% CI 1.014–1.172, $P=0.019$) were independent factors predictive of phosphate control (Table 5).

Factors associated with phosphate control in anuric patients

Only 31.8% ($N=14$) of the anuric patients achieved optimal phosphate control, although the frequency of using phosphate-binding agents was higher in the poor phosphate control group (90.3% vs. 58.3%, $P=0.028$). A detailed description of anuric HD patient characteristics, according to the phosphate control, is presented in Table 4.

In the univariate analysis model, LnFGF-23, $1,25(OH)_2D_3$, BUN, and creatinine levels were statistically significant; however, in the multivariate regression analysis, only LnFGF-23 (HR 2.894, 95% CI 1.294–6.474, $P=0.010$) was predictive of phosphate control (Table 5).

Discussion

Traditionally, the significance of RRF has been emphasized in peritoneal dialysis patients, but its importance has often been overlooked in HD patients. The significance of RRF in CKD-MBD in HD patients was first described by Viaene et al [13]. In their study, RRF was found to be an important determinant of FGF-23 and phosphate control in HD patients. Furthermore, Penne et al [14] reported in their study that GFR was negatively correlated with the phosphate binder dose in HD patients, and a GFR of >4.13 mL/minute/1.73 m^2 was an important predictor of adequate phosphate control.

Our study also demonstrated the significance of RRF for phosphate control in maintenance HD patients. Mineral metabolism was closer to normal physiology in the nonanuric patients than in the anuric patients; phosphate control was better, FGF-23 levels were significantly lower, and $1,25(OH)_2D_3$ levels were significantly higher in the nonanuric patients, and all these factors showed meaningful correlation with eGFR. This superiority of phosphate control in the nonanuric HD patients may be attributed to the occurrence of phosphaturia through the remnant nephron. In the nonanuric patients, excretion of phosphate through urine could inhibit further increase of serum FGF-23, and controlled FGF-23 secretion allowed the conversion of 25(OH)D to $1,25(OH)_2D_3$ [15].

The unique point of our study was that factors associated with phosphate control were found to differ according to the RRF status. For optimal phosphate control, FGF-23, as expected, was a significant factor in the anuric patients; however, in the nonanuric patients, BUN and GFR were the independent factors that were predictive of phosphate control, instead of FGF-23. Recently, Wang et al [16] reported data similar to that of our study. In their study of 134 maintenance HD patients, iPTH, FGF-23, and nPNA were the independent determinants of phosphate control in the anuric patients. For the nonanuric patients, only GFR and female sex were the independent determinants of phosphate control.

Traditionally, FGF-23 was regarded as a master regulator of phosphate homeostasis [17,18]. However, as observed in our and Wang et al's [16] studies, FGF-23 was not a determinant of phosphate control in the nonanuric HD patients. This might be the differences in the amount of phosphate excretion through the remnant nephron. In normal physiology, klotho, which is a membrane-bound cofactor that is required for binding FGF-23 to its receptor in the renal tubule [19], plays an important role in the FGF-23 action. However, in patients with maintenance HD, klotho level is already decreased and the amount of phosphaturia seems more likely to be dependent on GFR. Thus, GFR appears to be a fundamental factor for mineral metabolism in maintenance HD patients.

In this study, BUN was also a determinant of phosphate control in the nonanuric patients. Although BUN has an association with GFR as a filtration marker, it is also an important nutritional marker, especially for dietary phosphate. A higher BUN represents

Table 5. Regression analysis of factors relate to predialysis serum phosphate level, according to the residual renal function*

Variables	Univariate model			Multivariate model		
	HR	95% CI	*P*	HR	95% CI	*P*
Nonanuric patients						
LnFGF-23 (pg/mL)	2.539	1.170–5.511	0.018			
GFR (mL/min/1.73 m^2)	0.633	0.403–0.996	0.048	0.409	0.169–0.989	0.047
BUN (mg/dL)	1.090	1.020–1.164	0.011	1.090	1.014–1.172	0.019
Creatinine (mg/dL)	1.542	1.101–2.160	0.012			
Anuric patients						
LnFGF-23 (pg/mL)	2.064	1.135–3.754	0.018	2.894	1.294–6.474	0.010
$1,25(OH)_2D_3$ (pg/mL)	0.793	0.621–1.013	0.063			
BUN (mg/dL)	1.055	1.003–1.110	0.039			
Creatinine (mg/dL)	1.408	0.984–2.014	0.061			

* Adjusted age, sex, LnFGF-23, GFR, BUN, Cr, and fetuin A, in nonanuric patients. Adjusted age, sex, HT, LnFGF-23, BUN, Cr, $1.25(OH)_2D_3$ and use of sevelamer in anuric patients.

BUN, blood urea nitrogen; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; LnFGF-23, log-transformed fibroblast growth factor-23.

better nutritional status in maintenance HD patients [20]. Therefore, it is reasonable to assume that a higher BUN represents a higher dietary phosphate intake, and dietary intake is an important factor for phosphate control in nonanuric HD patients. nPNA and SGA were also measured as nutritional factors; however, they did not correlate with BUN in this study. The nPNA was measured using Bergström et al's [11] equation, which did not account for urinary protein loss, thus underestimating the nutrition status of nonanuric patients. SGA had several objective components; thus, slipshod attitude of the patients could incorrectly estimate nutritional status. A previous study also pointed out these problems [21]; thus, SGA could not reflect nutritional status correctly in this study.

FGF-23 and PTH stimulate phosphaturia in a similar manner by reducing phosphate reclamation through Na/Pi IIa, IIc cotransporters [8,9,18]. However, in our study, the role of iPTH in phosphate metabolism appeared to be less significant than that of FGF-23, and iPTH appeared to be less affected by RRF status, which is also consistent with the previous studies [13,14,16]. The reasons for these might be the combined regulation of calcium homeostasis in the CKD-MBD and complex interactions of FGF-23, iPTH, and 1,25 $(OH)_2D_3$ [22]. However, no clear relationships between FGF-23, iPTH, and RRF are revealed, thus warranting further investigation.

In our cross-sectional study, vascular calcification was not affected by RRF. Atherosclerosis is known to have a positive correlation with FGF-23 [23]; as serum FGF-23 levels were significantly higher in the anuric patients, we expected higher vascular calcification rates in those patients. Although CKD-MBD is one of the main factors for vascular calcification in dialysis patients [24,25], other factors, such as age, diabetes mellitus, hypertension, dialysis vintage, male gender, and calcification inhibitory factors (e.g., fetuin-A), are also closely associated with vascular calcification [26–29]. We were unable to establish a relationship between vascular calcification and RRF in our study. Further prospective observation studies are needed to address this point.

Our study has several limitations. First, we could not explain the cause and effect relationships between phosphate, RRF, FGF-23, 1,25$(OH)_2D_3$, and iPTH, because we did not measure the degree of phosphaturia in the nonanuric HD patients and did not control serum phosphate level in the anuric HD patients. Second, the sample size was small. Third, we did not control dietary phosphate during the study period. However, our results are consistent with previous data, and it is valuable to understand that phosphate metabolism is somewhat different according to RRF in HD patients.

In conclusion, RRF was found to be an important, possibly fundamental, factor for CKD-MBD in maintenance HD patients. In the anuric HD patients, FGF-23 was observed to be an important determinant of phosphate control; however, in nonanuric HD patients, GFR was more important than FGF-23 for phosphate control.

Conflicts of interest

All authors declare no competing interest.

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