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ORIGINAL ARTICLE

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Association of Mineral Bone Disorder With Decline in Residual Kidney Function in Incident Hemodialysis Patients

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ABSTRACT

Abnormalities of mineral bone disorder (MBD) parameters have been suggested to be associated with poor renal outcome in predialysis patients. However, the impact of those parameters on decline in residual kidney function (RKF) is uncertain among incident hemodialysis (HD) patients. We performed a retrospective cohort study in 13,772 patients who initiated conventional HD during 2007 to 2011 and survived 6 months of dialysis. We examined the association of baseline serum phosphorus, calcium, intact parathyroid hormone (PTH), and alkaline phosphatase (ALP) with a decline in RKF. Decline in RKF was assessed by estimated slope of renal urea clearance (KRU) over 6 months from HD initiation. Our cohort had a mean ± SD age of 62 ± 15 years; 64% were men, 57% were white, 65% had diabetes, and 51% had hypertension. The median (interquartile range [IQR]) baseline KRU level was 3.4 (2.0, 5.2) mL/min/1.73 m^2. The median (IQR) estimated 6-month KRU slope was −1.47 (−2.24, −0.63) mL/min/1.73 m^2 per 6 months. In linear regression models, higher phosphorus categories were associated with a steeper 6-month KRU slope compared with the reference category (phosphorus 4.0 to <4.5 mg/dL). Lower calcium and higher intact PTH and ALP categories were also associated with a steeper 6-month KRU slope compared with their respective reference groups (calcium 9.2 to <9.5 mg/dL; intact PTH 150 to <250 pg/mL; ALP <60 U/L). The increased number of parameter abnormalities had an additive effect on decline in RKF. Abnormalities of MBD parameters including higher phosphorus, intact PTH, ALP and lower calcium levels were independently associated with decline in RKF in incident HD patients. © 2019 American Society for Bone and Mineral Research. © 2019 American Society for Bone and Mineral Research.

KEY WORDS: PHOSPHORUS; RESIDUAL KIDNEY FUNCTION; PARATHYROID HORMONE; ALKALINE PHOSPHATASE; HEMODIALYSIS

Introduction

Loss of residual kidney function (RKF) among hemodialysis (HD) patients is associated with reduced survival, worsened anemia, malnutrition, and inflammation.[1–5] Over the past decade, more patients are initiating HD with a higher RKF and there is evidence suggesting beneficial effects of RKF on clinical outcomes in HD patients.[3,5–8] However, RKF declines at the fastest rate within the first several months after initiating dialysis.[9,10] Hence, preserving RKF has recently become an important therapeutic goal for patients starting dialysis.[5,6,8,11]

While it is well known that mineral bone disorder in chronic kidney disease (CKD-MBD) parameters results from loss of RKF, CKD-MBD may lead to further loss of RKF in a positive feedback loop, increasing morbidity and mortality in predialysis and

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dialysis patients.[12–17] The presence of hyperphosphatemia and secondary hyperparathyroidism (SHPT) has been shown to result in vascular calcifications, which in turn leads to advanced mortality and ischemic heart disease.[18–21] These vascular calcifications can also contribute to renal insufficiency in the setting of impaired renal blood flow, leading to further nephron damage. In addition, SHPT has been associated with decreased myocardial contractility, impaired insulin sensitivity, and glucose intolerance, which all may contribute to CKD progression.[22–25] There is also evidence that low serum calcium may be associated with progression of renal failure associated with vitamin D deficiency.[26–29] Furthermore, abnormal levels of vitamin D and fibroblast growth factor-23 (FGF-23), factors related to CKD-MBD homeostasis, may also play a role in renal damage.[30,31]

Over the last 20 years, there have been many advances in the treatment of CKD-MBD with the goal of decreasing mortality and improving cardiovascular health. It is still debatable whether targeting correction of CKD-MBD laboratory values is an adequate surrogate outcome for mortality and morbidity risks, but current guidelines continue to recommend achievement of target laboratory goals to mitigate these risks.[32] Keeping this limitation in mind, only one study has assessed the association between CKD-MBD lab abnormalities and loss of RKF among dialysis patients.[33] In a Dutch study of 1468 incident HD and peritoneal dialysis (PD) patients, Noordzij and colleagues found that disordered mineral metabolism was neither associated with the risk of becoming anuric nor with the rate of decline in RKF in dialysis patients.[33] The results of this study were surprising given existing animal models suggesting that serum phosphorous abnormalities may be responsible for an inflammatory reaction in the kidney leading to interstitial fibrosis and tubular atrophy with progressive loss of RKF.[34,35] Additionally, studies have also shown that phosphorous may cause direct nephrotoxicity, and elevated phosphorous levels can lead to calcium-phosphate crystal deposition in the nephron.[34,35] The null association findings in Noordzij's small study may be related to the crossing of phosphorus or calcium stratified RKF decline trajectories within several months after dialysis initiation[33] and the fact that RKF usually declines at the fastest rate within the first several months after dialysis initiation. Given these contradictory findings, we hypothesized that the abnormalities of MBD parameters after initiation of dialysis could affect early decline in RKF. Therefore, our study aims to investigate the associations between the CKD-MBD lab abnormalities (specifically phosphorous, calcium, parathyroid hormone [PTH], and alkaline phosphatase [ALP]) and the rate of decline in RKF among a large cohort of incident HD patients over the span of 6 months after dialysis initiation.

Materials and Methods

Subjects and data collection

We conducted a retrospective analysis of deidentified, incident, adult (18 years or older) conventional HD patients who maintained dialysis treatments for at least 60 consecutive days in a large dialysis organization in the United States between January 2007 and December 2011. Patients were followed from dialysis initiation until transplantation, discontinuation of dialysis, death, loss of follow-up, or December 31, 2011. Patient-quarters were made by dividing the follow-up time for each patient into 91-day periods from date of first dialysis. Conventional HD patients were defined as patients who received in-center HD and did not receive other dialysis modalities including nocturnal HD, peritoneal dialysis, home HD, less-frequent HD (≤2 times per week), or frequent HD (>3 times per week) for at least 45 days within the first patient-quarter. Patients with missing data on phosphorus and renal urea clearance (KRU) at baseline were excluded. We further excluded patients with a null value on baseline KRU and missing data on KRU at the third patient-quarter.

Demographic factors (age, sex, race/ethnicity, and primary insurance), cause of end-stage renal disease (ESRD), comorbidities (diabetes, hypertension, congestive heart failure, and cardiovascular disease), and laboratory variables (hemoglobin, albumin, phosphorus, calcium, intact PTH, ALP, and normalized protein catabolic rate [nPCR]) were obtained from data sets of the dialysis provider. Blood samples were collected predialysis. Because laboratory values were measured monthly except intact PTH (at least quarterly) and hemoglobin (more frequently), we averaged results within each patient-quarter to minimize measurement variability and utilized the first patient-quarter values as their baseline.

The study was approved by the Institutional Review Committee of the University of California, Irvine and exempted from informed consent.

Exposures and outcomes

The primary exposure was baseline serum phosphorus level, which we divided into eight exposure categories (<3.5, 3.5 to <4.0, 4.0 to <4.5, 4.5 to <5.0, 5.0 to <5.5, 5.5 to <6.0, 6.0 to <6.5, and ≥6.5 mg/dL). The primary outcome was a decline in RKF after 6 months from dialysis initiation. This was assessed using the slope of the KRU curve over time to determine rate of decline in RKF.

As secondary exposures, we assessed the association of other parameters of CKD-MBD including calcium, intact PTH, and ALP with 6-month KRU slope. We adjusted serum calcium levels for serum albumin levels and stratified the adjusted calcium levels into six categories (<8.4, 8.4 to <8.7, 8.7 to <9, 9 to <9.2, 9.2 to <9.5, and ≥9.5 mg/dL), intact PTH into six categories (<150, 150 to <250, 250 to <300, 300 to <400, 400 to <500, and ≥500 pg/mL), and ALP into six categories (<60, 60 to <75, 75 to <90, 90 to <105, 105 to <120, and ≥120 U/L). Serum albumin-adjusted calcium concentration (mg/dL) was calculated as [(4-serum albumin (g/dL)] × 0.8 + total serum calcium (mg/dL) when the serum albumin level was less than 4.0 g/dL. KRU was calculated using the formula below, adjusted for body surface area and expressed as mL/min/1.73 m^2.[36]

$$\mathrm{KRU}\,(\mathrm{mL/min}) = \frac{\text{Urinary urea nitrogen}\left(\frac{\mathrm{mg}}{\mathrm{dL}}\right) \times \text{urinary volume}\,(\mathrm{mL})}{\text{collected time}\,(\mathrm{min}) \times \left[0.9 \times \text{serum urea nitrogen}\left(\frac{\mathrm{mg}}{\mathrm{dL}}\right)\right]}$$

Statistical methods

For the baseline characteristics, continuous demographic, clinical, and laboratory variables were expressed as mean (± standard deviation [SD]) or median (interquartile range [IQR]) as appropriate. Nominal variables were expressed as proportions. The significance of trends across phosphorus categories were determined using a linear regression analysis or a nonparametric trend test, as appropriate.

Table 1. Baseline Characteristics of 13,772 Incident Hemodialysis Patients Stratified by Baseline Phosphorus

Variables	All patients	Serum phosphorus levels (mg/dL)								*p* Value
		<3.5	3.5 to <4.0	4 to <4.5	4.5 to <5	5 to <5.5	5.5 to <6	6 to <6.5	≥6.5	
n (%)	13,772	801 (6)	1438 (10)	2321 (17)	2684 (19)	2388 (17)	1756 (13)	1074 (8)	1310 (10)	
Age (years)	62 ± 15	69 ± 13	67 ± 13	65 ± 14	64 ± 14	61 ± 14	58 ± 14	56 ± 14	54 ± 14	<0.001
Male (%)	64	64	65	62	63	62	66	65	73	<0.001
Race/ethnicity (%)										
White	57	64	62	59	56	54	54	54	57	<0.001
African American	25	23	24	26	26	27	25	24	18	0.006
Hispanic	10	8	8	9	10	10	12	14	13	<0.001
Other	8	5	7	6	8	8	9	8	11	<0.001
Cause of ESRD (%)										
Diabetes	48	43	47	49	48	50	50	48	45	0.445
Hypertension	28	30	29	27	28	27	27	27	28	0.138
Glomerulonephritis	10	9	9	10	9	9	11	12	13	<0.001
Other	14	18	15	14	15	14	13	13	15	0.024
Primary insurance										
Medicare	50	59	57	55	52	50	45	43	41	<0.001
Medicaid	7	4	4	5	6	7	8	9	9	<0.001
Other	43	37	38	40	42	44	47	48	49	<0.001
Comorbidities (%)										
Diabetes	65	64	64	64	66	67	66	66	62	0.781
Hypertension	51	52	50	49	52	50	49	51	53	0.583
CHF	44	40	43	40	42	44	45	50	50	<0.001
CVD	24	26	26	25	26	24	23	22	21	<0.001
BMI (kg/m^2)	29.1 ± 7.4	28.7 ± 7.4	28.7 ± 7.3	28.8 ± 7.0	28.8 ± 7.2	29.7 ± 7.9	29.5 ± 7.4	29.5 ± 7.3	29.1 ± 7.7	<0.001
KRU (mL/min/1.73 m^2)	3.4 (2.0–5.2)	4.0 (2.0–6.6)	3.9 (2.2–6.1)	3.8 (2.1–5.9)	3.5 (2.1–5.3)	3.3 (2.0–5.0)	3.1 (1.9–4.8)	3.1 (1.8–4.6)	2.5 (1.5–3.7)	<0.001
Urine Volume (L/d)	0.9 (0.5–1.4)	0.7 (0.4–1.2)	0.8 (0.5–1.3)	0.9 (0.5–1.4)	0.9 (0.5–1.4)	1.0 (0.6–1.5)	1.0 (0.6–1.5)	1.0 (0.6–1.5)	1.0 (0.6–1.4)	<0.001
SBP change (mmHg)	31 ± 11	27 ± 11	29 ± 10	30 ± 11	30 ± 11	31 ± 12	31 ± 12	32 ± 11	33 ± 12	<0.001
Laboratory parameters										
Serum albumin (g/dL)	3.6 ± 0.4	3.5 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.5	3.6 ± 0.5	<0.001
Hemoglobin (g/dL)	11.4 ± 1.1	11.3 ± 1.1	11.4 ± 1.1	11.4 ± 1.1	11.5 ± 1.1	11.4 ± 1.0	11.5 ± 1.0	11.5 ± 1.1	11.4 ± 1.1	0.002
Calcium (mg/dL)	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.0 ± 0.6	9.0 ± 0.6	9.0 ± 0.6	<0.001
Intact PTH (pg/mL)	310 (204–467)	204 (139–301)	247 (165–344)	270 (181–391)	300 (201–440)	331 (221–485)	368 (250–558)	387 (256–556)	436 (295–649)	<0.001
ALP (U/L)	83 (66–107)	86 (68–111)	83 (66–107)	83 (67–108)	83 (67–108)	82 (66–106)	82 (66–105)	83 (65–108)	79 (64–102)	<0.001
nPCR (g/kg/d)	0.84 ± 0.21	0.71 ± 0.20	0.76 ± 0.18	0.79 ± 0.19	0.83 ± 0.19	0.85 ± 0.20	0.90 ± 0.21	0.92 ± 0.20	0.97 ± 0.24	<0.001
UFV (L)	1.9 (1.4–2.5)	1.7 (1.2–2.3)	1.8 (1.2–2.3)	1.8 (1.2–2.4)	1.8 (1.3–2.4)	1.9 (1.4–2.5)	2.0 (1.5–2.6)	2.1 (1.5–2.8)	2.3 (1.7–2.9)	<0.001
Weekly IDWG (%)	5.0 (3.4–6.7)	4.5 (2.9–6.2)	4.7 (3.2–6.5)	4.6 (3.1–6.4)	4.7 (3.3–6.4)	5.0 (3.4–6.8)	5.2 (3.6–6.8)	5.5 (3.8–7.3)	6.0 (4.4–7.7)	<0.001

ALP = alkaline phosphatase; BMI = body mass index; CHF = congestive heart failure; CVD = cardiovascular disease; ESRD = end-stage renal disease; IDWG = interdialytic weight gain; KRU = renal urea clearance; nPCR = normalized protein catabolic rate; PTH = parathyroid hormone; SBP = systolic blood pressure; UFV = ultrafiltration volume.

Values for categorical variables are shown as percentages; values for continuous variables as mean ± standard deviation or median (interquartile range).

Conversion factors for units: to convert albumin g/dL to g/L, multiply by 10; hemoglobin in g/dL to g/L, multiply by 10; calcium in mg/dL to mmol/L, multiply by 0.25; phosphorus in mg/dL to mmol/L, multiply by 0.323; intact PTH in pg/mL to ng/L, multiply by 1.0.

We estimated KRU slope over the first 6 months from dialysis initiation in patients with at least the quarterly average KRU in the first and third patient-quarters (± the second KRU patient-quarter) using a linear mixed-effects model allowing for a random intercept and slope and using an unstructured covariance matrix. To evaluate the association of categorized parameters of MBD with 6-month KRU slope, we performed a linear regression analysis. Four hierarchical models were examined: (1) an unadjusted; (2) a case mix-adjusted model that included age, sex, race/ethnicity (white, African American, Hispanic, or other), primary insurance (Medicare, Medicaid, or other), cause of ESRD (diabetes, hypertension, glomerulonephritis, or other), and comorbidities (diabetes, hypertension, congestive heart failure, and cardiovascular disease); (3) an expanded case mix-adjusted model that additionally included baseline KRU; and (4) a fully adjusted model that included all of the above variables plus maximal change in systolic blood pressure (SBP) (predialysis SBP—lowest SBP during HD), body mass index (BMI), hemoglobin, albumin, nPCR, ultrafiltration volume (UFV), and weekly interdialytic weight gain (IDWG) as well as MBD parameters other than the exposure of interest (ie, phosphorus, calcium, intact PTH, and ALP). nPCR was calculated taking into account RKF.[37]

A restricted cubic spline model with four knots was used for examining the association of the outcome with MBD parameters as continuous variables. For sensitivity analysis, to examine the association of serum phosphorus with another surrogate marker of RKF, we assessed 6-month change in urine volume using a linear regression model adjusted for covariates. Hemoglobin, albumin, calcium, intact PTH, ALP, and nPCR had missing data (<1.0% for all variables). Baseline missing data were imputed using multiple imputation with five imputed data sets in a linear regression model.

To assess the effect modifications by age, nutritional status, baseline RKF, and fluid status on the association of phosphorus with 6-month KRU slope, we performed likelihood ratio testing by adding an interaction term between phosphorus and each of the covariates (age, serum albumin, baseline KRU, UFV, and IDWG) to the linear regression model, and then did subgroup analyses with categories of phosphorus <3.5, 3.5 to <5.5 (reference), and ≥5.5 mg/dL according to age (≥70 or <70 years old), serum albumin (≥3.8 or <3.8 g/dL), baseline KRU (≥3 or <3 mL/min/1.73 m^2), UFV (≥2.0 or <2.0 L), and weekly IDWG (≥6% or <6%).

Similarly, we evaluated the association of 6-month KRU slope with the number of abnormalities (zero, one, two, or three) in MBD parameters including phosphorus, calcium, and intact PTH using linear regression analyses. Abnormal phosphorus, calcium, and intact PTH concentrations were defined as levels of serum phosphorus <3.5 or >5.5 mg/dL, calcium <8.4 or >9.5 mg/dL, and intact PTH < 150 or >300 pg/mL, respectively. The PTH cut-off was based on targets recommended in the 2003 Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.[38] All statistical analyses were conducted using STATA, version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

We identified 41,768 incident HD patients with data on baseline serum phosphorus and KRU from 147,273 patients who were assigned to conventional HD. After further excluding patients with a null value on baseline KRU (n = 173) and missing data on KRU at the third patient-quarter (n = 27,996), we finally included 13,772 patients (Supplemental Fig. S1). Our cohort had a mean ± SD age of 62 ± 15 years; 64% were men, 57% were white, 25% were African American, 65% had diabetes, and 51% had hypertension (Table 1). The mean ± SD baseline phosphorus and calcium levels were 5.0 ± 1.1 mg/dL and 9.1 ± 0.5 mg/dL, respectively. The median (IQR) of baseline intact PTH, ALP, and KRU levels were 310 (204, 467) pg/mL, 83 (66, 107) U/L, and 3.4 (2.0, 5.2) mL/min/1.73 m^2, respectively.

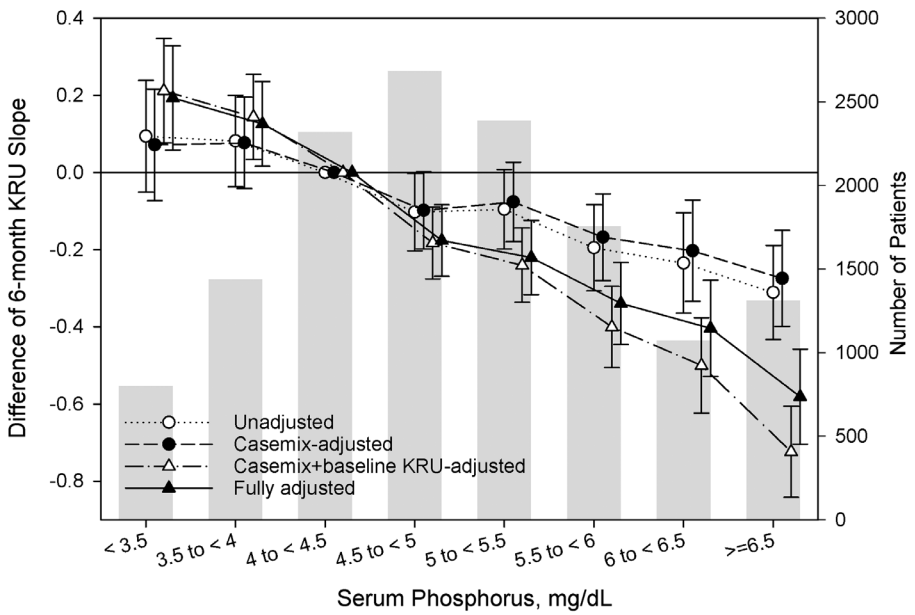

Fig. 1. The association of baseline serum phosphorus levels with 6-month renal urea clearance (KRU) slope among 13,772 incident hemodialysis patients.

Association of phosphorus with an estimated slope of KRU

The median (IQR) of estimated 6-month KRU slope was −1.47 (−2.24, −0.63) mL/min/1.73 m^2 per 6 months. In linear regression models, higher phosphorus categories were associated with steeper 6-month KRU slope (ie, greater decline in RKF) (Fig. 1). The association between phosphorus as a continuous variable and 6-month KRU slope was also robust in restricted cubic spline models (Supplemental Fig. S2).

In subgroup analyses, the association between serum phosphorus and decline in RKF was not modified by nutritional status assessed by serum albumin ($P_{interaction}$ = 0.273); phosphorus <3.5 mg/dL was associated with a gentler KRU slope and phosphorus ≥5.5 mg/dL was associated with a steeper KRU slope compared with phosphorus 3.5 to <5.5 mg/dL. Subgroup analyses according to UFV ($P_{interaction}$ = 0.07) and weekly IDWG ($P_{interaction}$ = 0.54) also showed consistent results. However, the association of phosphorus and decline in RKF was modified by age ($P_{interaction}$ < 0.001) and baseline KRU ($P_{interaction}$ < 0.001), whereas the association of lower phosphorus with a gentle KRU slope was modestly attenuated among patients over the age of 70 years old and with baseline KRU < 3 mL/min/1.73 m^2 (Fig. 2).

Sensitivity analyses using 6-month change in urine volume as another index of RKF

The median (IQR) of baseline urine volume was 900 (500, 1400) mL/d, and the mean ± SD change in urine volume after 6 months was −171 ± 637 mL/d. Higher phosphorus levels were associated with greater loss in urine volume after 6 months compared with the reference (Fig. 3). The highest phosphorus group (≥6.5 mg/dL) had 221 mL loss in urine volume after 6 months compared with the reference group (phosphorus 4.0 to <4.5 mg/dL).

Association of calcium, intact PTH, and ALP with an estimated slope of KRU

Lower calcium categories were associated with a greater decline in RKF after 6 months from HD initiation compared with the reference category (calcium 9.2 to <9.5 mg/dL) (Fig. 4*A*).

Fig. 4*B* shows unadjusted and adjusted beta coefficients (βs) and 95% confidence intervals (CIs) of 6-month KRU slope associated with intact PTH categories (n = 13,729). Compared with intact PTH 150 to <250 pg/mL, intact PTH levels ≥400 pg/mL were associated with a steeper KRU slope, even after adjustment for phosphorus, calcium, and ALP. Higher ALP was also associated with a faster decline in RKF; compared with ALP <60 U/L, higher ALP categories were associated with a greater magnitude of 6-month KRU slope in the fully adjusted model (Fig. 4*C*).

In restricted cubic spline models, the associations between continuous calcium, intact PTH, and ALP and 6-month KRU slope were still robust (Supplemental Fig. S3).

The association of the number of phosphorus, calcium, and intact PTH abnormalities with 6-month KRU slope

Compared with patients with normal values for all three MBD parameters (calcium, phosphorus, and intact PTH), a higher number of abnormal parameters was associated with a greater decline in RKF; the fully adjusted βs (95% CI) of 6-month KRU slope were 0.09 (0.01–0.17), 0.23 (0.15–0.32), and 0.31 (0.19–0.43) at the number of abnormal parameters of one, two, and three, respectively (Fig. 5).

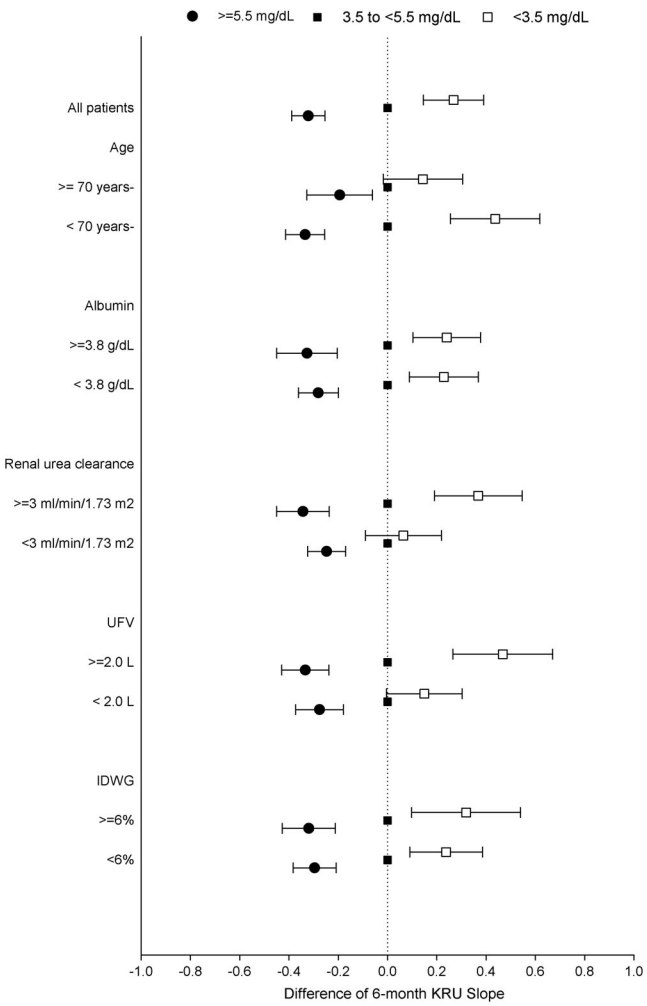

Fig. 2. Overall and subgroup analyses of association between baseline serum phosphorus levels and 6-month renal urea clearance (KRU) slope in the fully adjusted model. Points and bars represent beta coefficients and 95% confidence intervals, respectively. Reference is serum phosphorus 3.5 to <5.5 mg/dL. UFV = ultrafiltration volume; IDWG = interdialytic weight gain.

Discussion

In this study, we demonstrated that higher serum phosphorus levels were associated with greater decline in RKF during 6 months post dialysis initiation among HD patients. We also found that higher intact PTH and ALP and lower serum calcium levels were associated with a greater decline in RKF. Furthermore, the greater number of MBD parameters deviating from guideline-recommended concentrations was associated with a steeper 6-month KRU slope.

Our findings showing the association between hyperphosphatemia and poor renal outcome in HD patients are in line with those of previous animal researches and studies of

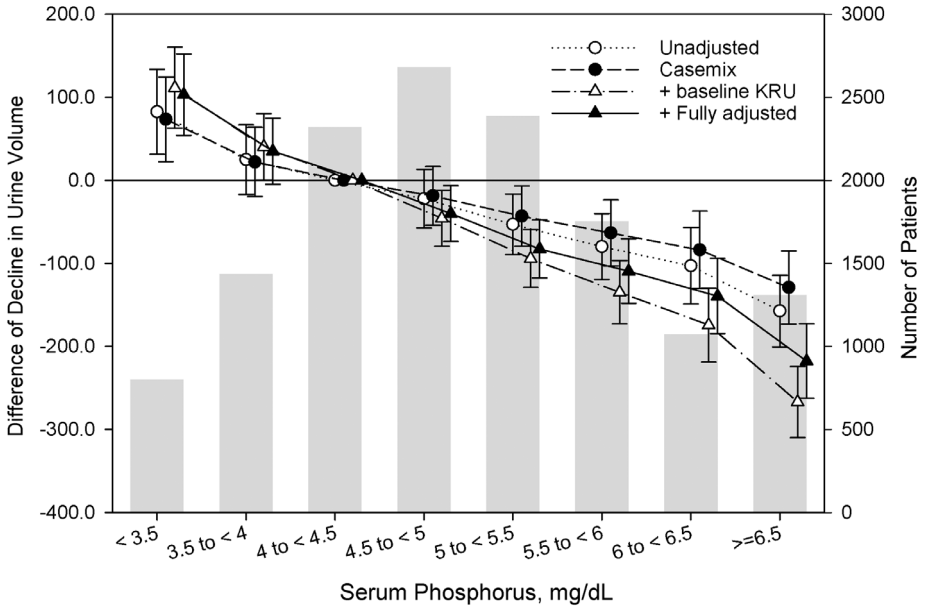

Fig. 3. The association of baseline serum phosphorus levels with 6-month change in urine volume among 13,772 incident hemodialysis patients.

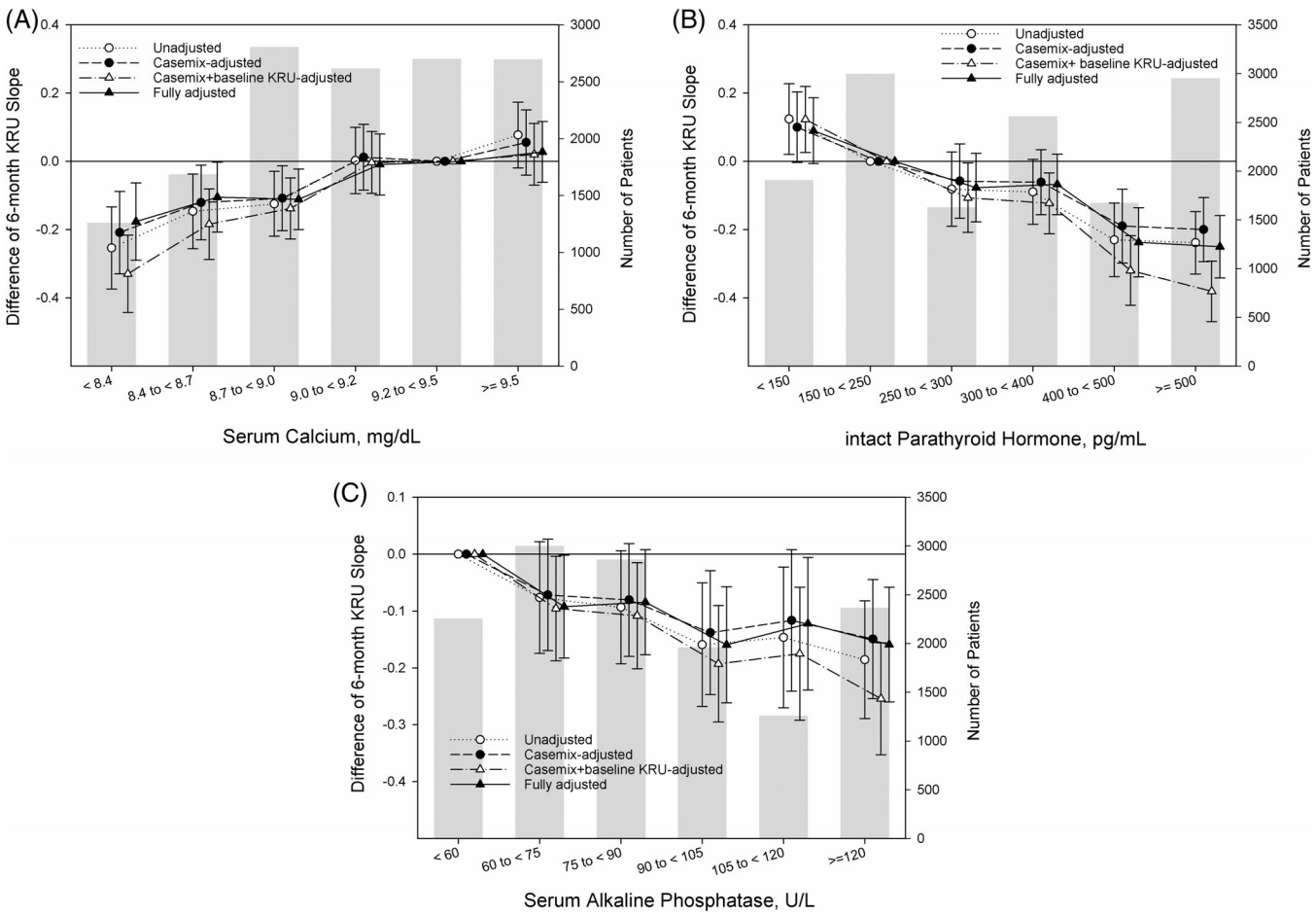

Fig. 4. The association of 6-month renal urea clearance (KRU) slope with serum calcium (*A*), intact parathyroid hormone (*B*), and alkaline phosphatase (*C*) in incident hemodialysis patients.

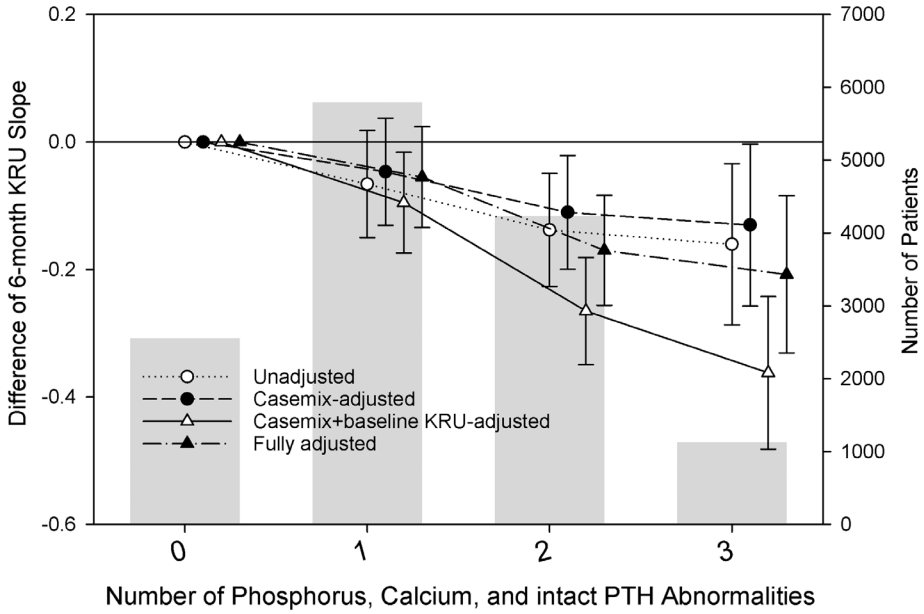

Fig. 5. The association of number of phosphorus, calcium, and intact PTH abnormalities with 6-month slope of KRU among 13,772 incident hemodialysis patients.

predialysis CKD patients.[17,34,35] Interestingly, contrary to intuition that a higher serum calcium concentration would be associated with a rapid decline in RKF, there is some evidence of the association between lower serum calcium and rapid CKD progression among nondialysis patients with CKD.[26,27,39] However, the association between serum calcium and decline in RKF was uncertain in HD patients. In this study, we observed that lower serum calcium levels were associated with more rapid decline in RKF among incident HD patients. These results remained robust even after adjusting for other MBD parameters and baseline RKF. The potential mechanism explaining the association of hypocalcemia with poor renal outcomes is unclear. However, previous studies have suggested that vitamin D deficiency resulting in hypocalcemia may be associated with CKD progression. Low levels of 25-hydroxyvitamin D3 or 1,25-dihydroxyvitamin D3 were associated with increased risk for ESRD in advanced CKD patients.[28,29]

Contrary to our results, which showed a significant association of serum phosphorus and calcium with decline in RKF, the study by Noordzij and colleagues did not demonstrate that disturbance of serum phosphorus and calcium leads to a faster decline in RKF among dialysis patients.[33] The discrepancies between their results and ours may be related to cohort differences. In Noordzij's study of 1468 HD patients, more than 40% of HD patients had no significant comorbidity and had relatively low prevalence of diabetic kidney disease (16%), which may have implications for the decline rate of RKF in their cohort. Moreover, because only 7% of 899 HD patients had serum calcium levels <8.4 mg/dL in their study (versus 1261 [9.2%] in the present study), the effect of hypocalcemia on RKF could not have been properly revealed.

With regard to PTH and SHPT, our study showed that higher PTH values were associated with a greater decline in RKF. Interestingly, Noordzij's study suggested an opposing association in which high PTH values were associated with a decreased risk of becoming anuric.[33] Based upon the 2017 KDIGO guidelines for CKD-MBD that recommend maintaining PTH values 2 to 9 times the upper limit of normal, the results of our study would suggest that although there does not appear to be any difference in mortality outcomes with maintaining elevated PTH values, the association with decreased RKF may result in other comorbid conditions.[32]

Although ALP is typically less utilized in assessing CKD-MBD markers compared with our other more established markers (ie, calcium, phosphorus, and intact PTH), serum ALP is usually elevated in dialysis patients with high-turnover bone disease.[40] ALP has been associated with coronary artery and other vasculature calcifications potentially leading to a decrease in RKF.[41,42] Our study results are in line with this hypothesis and show that higher ALP levels are associated with a greater decline in RKF. Therefore, early monitoring of ALP levels upon dialysis initiation may be helpful for not only evaluating bone disease but also predicting RKF decline.

In our study, abnormalities in all three traditional CKD-MBD markers were associated with greater RKF loss in HD patients. These results may suggest a need for more comprehensive management of MBD in HD patients, or alternatively may reflect problems in adherence to dialysis treatments and phosphorous binders in HD patients. The latter being an area that we were unable to assess and adjust for and is thereby one of the limitations of our study.

There are several other limitations to be mentioned in our study. First, although we adjusted for potential confounders in our investigation of the association between MBD parameters and decline in RKF, residual confounding may remain. Patients with a disordered mineral metabolism at dialysis initiation may be in poor health, necessitating aggressive interventions including fluid overload and stringent volume control. The

combination of poor health and aggressive interventions may be associated with a decline in RKF. However, high phosphorus levels were independently associated with a decline in RKF even after adjusting for UFV and weekly IDWG (markers of fluid overload). Moreover, when we repeated the analysis with a focus on 6 to 12 months post-initiation of dialysis, the association between high phosphorus and decline in RKF had a similar trend suggesting that the mechanism of injury resulting in the decline in RKF continues over time and is not a phenomenon limited to the 6-month period after dialysis initiation (Supplemental Fig. S4). Second, potential selection bias introduced by the inclusion of only patients with KRU data at baseline and the third patient-quarter may be another limitation of our study. Patients who have little or no RKF at baseline and have rapid loss of RKF are less likely to collect their urine output to measure KRU, which might result in the exclusion from this study. However, in additional analyses looking at those who were included and excluded in the study due to lack of RKF data, there were no remarkable differences in baseline characteristics potentially suggesting that they were missing at random (Supplemental Table S1). Third, we calculated KRU with predialysis serum urea concentration according to the approach by Daugirdas and colleagues.[36] This method may cause concern that KRU can be underestimated. However, a recent study by Obi and colleagues compared KRU equations and found that KRU estimates from dividing urinary urea nitrogen by 0.9 × predialysis serum urea nitrogen had a lower degree of bias compared with an equation that used the average of serum urea nitrogen values at the start and end of the urine collection period.[43] Furthermore, as we recognize that increased protein intake can also raise both phosphorus and serum urea nitrogen levels potentially strengthening the association between high phosphorus levels and RKF, we attempted to address this limitation by adjusting for nutritional status as assessed by albumin levels and nPCR. The relationship between phosphorus and decline in RKF remained robust despite adjustment for albumin and nPCR, suggesting that there may be a true association between phosphorus and a decline in RKF. Notwithstanding some limitations, our results put forward evidence that controlling abnormal MBD parameters is important for the preservation of RKF in incident HD patients.

In conclusion, higher phosphorus, higher intact PTH, higher ALP, and lower calcium levels were independently associated with greater decline in RKF in incident HD patients. Our results highlight the potential benefit of MBD parameter control for the preservation of RKF of patients when initiating HD. Further clinical trials are needed to confirm and elucidate a causal effect of MBD parameters on RKF among incident HD patients.

Disclosures

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References

1. Pecoits-Filho R, Heimburger O, Barany P, et al. Associations between circulating inflammatory markers and residual renal function in CRF patients. Am J Kidney Dis. 2003;41(6):1212–8.
2. Suda T, Hiroshige K, Ohta T, et al. The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. Nephrol Dial Transplant. 2000;15(3):396–401.
3. Penne EL, van der Weerd NC, Grooteman MP, et al. Role of residual renal function in phosphate control and anemia management in chronic hemodialysis patients. Clin J Am Soc Nephrol. 2011;6(2):281–9.
4. Termorshuizen F, Dekker FW, van Manen JG, et al. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004;15(4):1061–70.
5. Obi Y, Rhee CM, Mathew AT, et al. Residual kidney function decline and mortality in incident hemodialysis patients. J Am Soc Nephrol. 2016;27(12):3758–68.
6. US Renal Data System 2015 annual data report. Chapter 1: incidence, prevalence, patient characteristics, and treatment modalities. Am J Kidney Dis. 2016;67(3):S139–58.
7. Paniagua R, Santos D, Munoz R, Luengas J, Frenk S. Renal-function in protein-energy malnutrition. Pediatr Res. 1980;14(11):1260–2.
8. Marquez IO, Tambra S, Luo FY, et al. Contribution of residual function to removal of protein-bound solutes in hemodialysis. Clin J Am Soc Nephrol. 2011;6(2):290–6.
9. Jansen MA, Hart AA, Korevaar JC, et al. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002;62(3):1046–53.
10. de Jager DJ, Halbesma N, Krediet RT, et al. Is the decline of renal function different before and after the start of dialysis? Nephrol Dial Transplant. 2013;28(3):698–705.
11. Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis. 2010;56(2):348–58.
12. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15(8):2208–18.
13. Young EW, Akiba T, Albert JM, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2004;44(5 Suppl 2):34–8.
14. Voormolen N, Noordzij M, Grootendorst DC, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909–16.
15. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Outcomes associated with serum phosphorus level in males with non-dialysis dependent chronic kidney disease. Clin Nephrol. 2010;73(4):268–75.
16. Bellasi A, Mandreoli M, Baldrati L, et al. Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-

moderate kidney dysfunction. Clin J Am Soc Nephrol. 2011;6(4): 883–91.

17. Da J, Xie X, Wolf M, et al. Serum phosphorus and progression of CKD and mortality: a meta-analysis of cohort studies. Am J Kidney Dis. 2015;66(2):258–65.
18. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–83.
19. Okuno S, Ishimura E, Kitatani K, et al. Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2007;49(3):417–25.
20. Reynolds JL, Joannides AJ, Skepper JN, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol. 2004;15(11):2857–67.
21. Di Marco GS, Konig M, Stock C, et al. High phosphate directly affects endothelial function by downregulating annexin II. Kidney Int. 2013; 83(2):213–22.
22. Massry SG, Smogorzewski M. Mechanisms through which parathyroid hormone mediates its deleterious effects on organ function in uremia. Semin Nephrol. 1994;14(3):219–31.
23. Chiu KC, Chuang LM, Lee NP, et al. Insulin sensitivity is inversely correlated with plasma intact parathyroid hormone level. Metabolism. 2000;49(11):1501–5.
24. Schumock GT, Andress DL, Marx SE, Sterz R, Joyce AT, Kalantar-Zadeh K. Association of secondary hyperparathyroidism with CKD progression, health care costs and survival in diabetic predialysis CKD patients. Nephron Clin Pract. 2009;113(1):c54–61.
25. Asche CV, Marx SE, Kim J, Unni SK, Andress D. Impact of elevated intact parathyroid hormone on mortality and renal disease progression in patients with chronic kidney disease stages 3 and 4. Curr Med Res Opin. 2012;28(9):1527–36.
26. Lim LM, Kuo HT, Kuo MC, et al. Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients. BMC Nephrol. 2014;15:183.
27. Janmaat CJ, van Diepen M, Gasparini A, et al. Lower serum calcium is independently associated with CKD progression. Sci Rep. 2018;8(1): 5148.
28. Melamed ML, Astor B, Michos ED, Hostetter TH, Powe NR, Muntner P. 25-hydroxyvitamin D levels, race, and the progression of kidney disease. J Am Soc Nephrol. 2009;20(12):2631–9.
29. Kendrick J, Cheung AK, Kaufman JS, et al. Associations of plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations with death and progression to maintenance dialysis in patients with advanced kidney disease. Am J Kidney Dis. 2012;60(4):567–75.
30. de Borst MH, Vervloet MG, ter Wee PM, Navis G. Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF-23-klotho in chronic kidney disease. J Am Soc Nephrol. 2011;22(9): 1603–9.
31. Cozzolino M, Gentile G, Mazzaferro S, Brancaccio D, Ruggenenti P, Remuzzi G. Blood pressure, proteinuria, and phosphate as risk factors for progressive kidney disease: a hypothesis. Am J Kidney Dis. 2013; 62(5):984–92.
32. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int. 2017;92(1):26–36.
33. Noordzij M, Voormolen NM, Boeschoten EW, et al. Disordered mineral metabolism is not a risk factor for loss of residual renal function in dialysis patients. Nephrol Dial Transplant. 2009;24(5):1580–7.
34. Koizumi T, Murakami K, Nakayama H, Kuwahara T, Yoshinari O. Role of dietary phosphorus in the progression of renal failure. Biochem Biophys Res Commun. 2002;295(4):917–21.
35. Khan SR. Crystal-induced inflammation of the kidneys: results from human studies, animal models, and tissue-culture studies. Clin Exp Nephrol. 2004;8(2):75–88.
36. Daugirdas JT. Physiologic principles and urea kinetic modeling. In Daugirdas JT, Blake PG, Ing TS, eds. Handbook of dialysis. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.
37. Depner TA, Daugirdas JT. Equations for normalized protein catabolic rate based on two-point modeling of hemodialysis urea kinetics. J Am Soc Nephrol. 1996;7(5):780–5.
38. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42(4 Suppl 3):S1–201.
39. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825–31.
40. Sardiwal S, Magnusson P, Goldsmith DJ, Lamb EJ. Bone alkaline phosphatase in CKD-mineral bone disorder. Am J Kidney Dis. 2013;62(4): 810–22.
41. Lomashvili KA, Garg P, Narisawa S, Millan JL, O'Neill WC. Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. Kidney Int. 2008;73(9): 1024–30.
42. Shantouf R, Kovesdy CP, Kim Y, et al. Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2009;4(6):1106–14.
43. Obi Y, Kalantar-Zadeh K, Streja E, Daugirdas JT. Prediction equation for calculating residual kidney urea clearance using urine collections for different hemodialysis treatment frequencies and interdialytic intervals. Nephrol Dial Transplant. 2018;33(3):530–9.