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Hyperphosphatemia is a combined function of high serum PTH and high dietary protein intake in dialysis patients

Elani Streja[1,8], Wei Ling Lau[1,8], Leanne Goldstein[1], John J. Sim[2], Miklos Z. Molnar[1], Allen R. Nissenson[3,4], Csaba P. Kovesdy[5,6] and Kamyar Kalantar-Zadeh[1,7]

[1]*Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine School of Medicine, Orange, California, USA;* [2]*Kaiser Permanente, Los Angeles, California, USA;* [3]*DaVita, El Segundo, California, USA;* [4]*David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, California, USA;* [5]*University of Tennessee Health Science Center, Memphis, Tennessee, USA;* [6]*Memphis VA Medical Center, Memphis, Tennessee, USA and* [7]*Department of Epidemiology, UCLA School of Public Health, Los Angeles, California, USA*

Elevated serum phosphorus is associated with higher death risk in hemodialysis patients. Previous studies have suggested that both higher serum parathyroid hormone (PTH) level and higher dietary protein intake may contribute to higher serum phosphorus levels. However, it is not well known how these two factors simultaneously contribute to the combined risk of hyperphosphatemia in real patient-care scenarios. We hypothesized that the likelihood of hyperphosphatemia increases across higher serum PTH and higher normalized protein catabolic rate (nPCR) levels, a surrogate of protein intake. Over an 8-year period (July 2001–June 2009), we identified 69,355 maintenance hemodialysis patients with PTH, nPCR, and phosphorus data in a large dialysis provider. Logistic regression models were examined to assess the association between likelihood of hyperphosphatemia (serum phosphorus >5.5 mg/dl) and serum PTH and nPCR increments. Patients were 61 ± 15 years old and included 46% women, 33% blacks, and 57% diabetics. Both higher serum PTH level and higher protein intake were associated with higher risk of hyperphosphatemia in dialysis patients. Compared with patients with PTH level 150–$<$300 pg/ml and nPCR level 1.0–$<$1.2 g/kg/day, patients with iPTH $>$ 600 pg/ml and nPCR $>$ 1.2 g/kg/day had a threefold higher risk of hyperphosphatemia (OR: 3.17, 95% CI: 2.69–3.75). Hyperphosphatemia is associated with both higher dietary protein intake and higher serum PTH level in maintenance hemodialysis patients. Worsening or resistant hyperphosphatemia may be an under-appreciated consequence of secondary hyperparathyroidism independent of dietary phosphorus load. Management of hyperphosphatemia should include diligent correction of hyper-parathyroidism while maintaining adequate intake of high protein foods with low phosphorus content.

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Correspondence: *Kamyar Kalantar-Zadeh, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine, School of Medicine, 101 The City Drive South, City Tower, Suite 400—ZOT: 4088, Orange, California 92868-3217, USA. E-mail: kkz@uci.edu*

[8]These authors contributed equally to this work.

Hyperphosphatemia is a common disorder in individuals with chronic kidney disease (CKD) and results from impaired renal phosphorus clearance and abnormal bone remodeling, in the face of continued intestinal absorption and poor outcomes.[1–8] The phosphatonins, or hormonal regulators of phosphorus balance, include 1,25-dihydroxyvitamin D, fibroblast growth factor 23 (FGF23) with its cofactor klotho, and parathyroid hormone (PTH).[9] It is noteworthy that phosphorus loading occurs early in CKD stage 3, as evidenced by increased serum levels of FGF23, which precedes rise in PTH or phosphorus levels.[10] Numerous observational studies have associated hyperphosphatemia with increased risk of CKD and mortality both in the general population[1] and in patients with CKD[11,12] and those on maintenance dialysis.[13–16] Elevated serum phosphorus likely contributes to cardiovascular disease and death via promotion of vascular calcification. Elevated phosphate drives osteogenic phenotype change[17,18] and apoptosis[19,20] pathways leading to mineralization of vascular smooth muscle cells *in vitro*, and dietary phosphate loading in rodent CKD models increases aortic calcification.[21,22] Furthermore, hyperphosphatemia may worsen the rate of CKD progression.[23,24]

Because correction and prevention of hyperphosphatemia is a mainstay of CKD management, therapeutic interventions consist of dietary phosphorus restriction, the use of phosphorus binders, and dialysis. As foods high in protein are a major source of dietary phosphorus, it is plausible that increasing protein intake may contribute to hyperphosphatemia. Indeed,

decreased protein intake has been correlated with low serum phosphorus and relatively low PTH levels in elderly dialysis patients.[25] Normalized protein nitrogen appearance (nPNA; also referred to as normalized protein catabolic rate (nPCR)) is a commonly used measurement of protein intake in maintenance hemodialysis (MHD) patients. Previous studies have correlated increased dietary phosphate/protein ratio[26] and extremes of nPCR (<0.8 or >1.4 g/kg/day)[27] with increased mortality, although the predictive value of nPCR on serum phosphorus levels appears more complex[28] and has not been well examined.

Control of secondary hyperparathyroidism, another treatment goal in CKD, is often overlooked as an additional therapeutic intervention that impacts serum phosphorus levels. Elevated PTH feeds into abnormal bone turnover such that the skeleton cannot perform its normal function as a reservoir for excess circulating mineral.[9] Results from the OPTIMA trial were recently reported, whereby MHD patients with secondary hyperparathyroidism (PTH levels 300–799 pg/ml) were randomized to conventional therapy with activated vitamin D and/or phosphate binders versus a cinacalcet-based regimen.[29] The OPTIMA trial found that serum phosphorus control was improved when PTH was effectively lowered, irrespective of treatment strategy. Further evidence for pathological effects of elevated PTH in CKD comes from the studies by Wesseling-Perry *et al.*,[30] whereby intravenous PTH infusion raised serum phosphorus levels in MHD patients but lowered serum phosphorus in healthy volunteers.[30]

Given that both nPCR and elevated PTH influence serum phosphorus levels, we propose using both parameters simultaneously as a 'bivariate' predictor of hyperphosphatemia risk. We tested our hypothesis with a large and contemporary cohort of MHD patients.

RESULTS

Baseline characteristics

Over the 5-year period (July 2001–June 2006), 164,789 subjects received dialysis treatment in units owned by DaVita (Figure 1). After deleting those patients who did not maintain at least 45 days of thrice-weekly hemodialysis treatment during the base calendar quarter or those who had missing core values (age, dialysis vintage, iPTH, nPCR, and serum phosphorus), 69,355 hemodialysis patients remained. Baseline characteristics of the 69,355 patients stratified by baseline iPTH and nPCR level are presented in Table 1. Patients with combined higher iPTH and nPCR level tended to be younger males who had longer dialysis duration, less prevalence of diabetes, and other comorbidities: congestive heart failure, atherosclerotic disease, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and other cardiovascular disease. They also tended to have better nutrition inflammation status with a higher serum albumin and creatinine level and were less likely to be white patients.

Figure 2 illustrates the combined (three-dimensional) association of serum iPTH and nPCR with the odds of a serum phosphorus >5.5 g/dl. As shown in Figure 2, the odds of a serum phosphorus >5.5 g/dl increases linearly with increasing serum iPTH, and there is an increasing trend towards hyperphosphatemia with increments of nPCR. Overall, combined higher serum iPTH level and higher protein intake were associated with higher risk of hyperphosphatemia in dialysis patients. This trend is steeper with increasing nPCR concentrations up to about 1.0 g/kg/day.

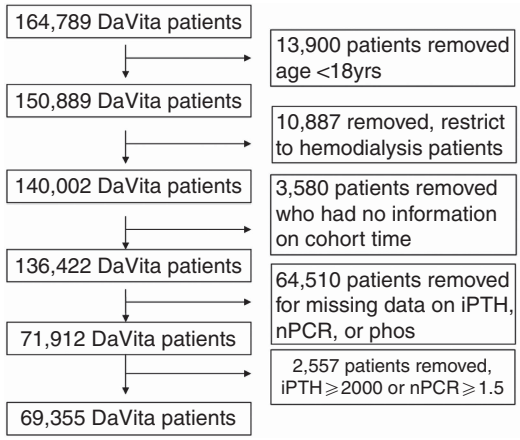

Figure 1 | Algorithm (flow chart) of patient selection for the cohort. iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; phos, phosphorus.

To further study the combined predictive effect of nPCR and serum iPTH on hyperphosphatemia, we created 16 groups combining 4 levels of nPCR with 4 levels of serum iPTH. As shown in Figure 3, using patients with iPTH level 150–<300 pg/ml and nPCR level 1.0–<1.2 g/kg/day as a reference group, patients with iPTH >600 pg/ml and nPCR $\geqslant 1.2$ g/kg/day had a threefold higher risk of hyperphosphatemia (OR: 3.17, 95% CI: 2.69–3.75) in fully adjusted models. This figure shows an increasing risk for hyperphosphatemia with increasing levels of iPTH and across increasing levels of serum nPCR. Odds of hyperphosphatemia level per group were similar across unadjusted, case-mix, and case-mix and MICS fully adjusted analyses. Alternative analysis, including modeling hyperphosphatemia across increments of protein intake (nPCR) within subgroups of iPTH levels, resulted in similar trends (see Figure 4).

In Table 2, we demonstrate predicted values for serum phosphorus for a white non-diabetic male aged 60 years based on three levels of adjustment: unadjusted, case-mix, case-mix and MICS. This table similarly demonstrates increasing levels of predicted serum phosphorus with increasing levels of iPTH and additionally increasing across increasing levels of nPCR.

DISCUSSION

In this large and contemporary cohort of 69,355 MHD patients, we validated that both nPCR and intact PTH levels were significant and independent predictors of hyperphosphatemia. When considered simultaneously, nPCR

Table 1 | Baseline demographic, clinical, and laboratory variables according to four groups of parathyroid hormone and protein catabolic rate in 69,355 maintenance hemodialysis patients

Variable	Total (*n*=69,355)	PTH<300; nPCR<1.0 (*n*=26,813)	PTH<300; nPCR≥1.0 (*n*=16,468)	PTH300; nPCR<1.0 (*n*=14,920)	PTH300; nPCR≥1.0 (*n*=11,154)	ANOVA	REG
Mortality (%)	65	69	63	63	56	<0.0001	<0.0001
Age (years)	62 ± 15	64 ± 15	63 ± 14	59 ± 16	57 ± 15	<0.0001	<0.0001
Gender (% women)	46	46	44	48	44	<0.0001	0.062
Diabetes mellitus (%)	57	69	62	53	53	<0.0001	<0.0001
Race (%)							
White	40	47	43	32	29	<0.0001	<0.0001
African-American	33	29	22	47	38	<0.0001	<0.0001
Hispanic	16	14	20	12	20	<0.0001	<0.0001
Asian	3	2	5	1	4	<0.0001	0.0018
Other	8	8	10	8	9	<0.0001	0.0002
Marital status (%)							
Married	35	35	40	30	34	<0.0001	<0.0001
Divorce	6	6	6	7	7	<0.0001	<0.0001
Single	20	18	17	25	25	<0.0001	<0.0001
Widow	12	14	12	12	9	<0.0001	<0.0001
Missing	27	27	25	26	25	<0.0001	<0.0001
Primary insurance (%)							
Medicare	61	61	61	60	59	0.0004	0.0005
Medicaid	6	5	5	6	7	<0.0001	<0.0001
Private insurance	14	14	16	13	15	<0.0001	0.0515
Other	8	7	6	9	8	<0.0001	0.0042
Missing	12	13	11	12	10	<0.0001	<0.0001
Vintage (time on dialysis) (%)							
3–6 months	14	18	11	15	11	<0.0001	<0.0001
6–12 months	17	20	16	17	13	<0.0001	<0.0001
2–5 years	40	41	42	38	38	<0.0001	<0.0001
>5 years	28	21	31	30	38	<0.0001	<0.0001
Kt/V (dialysis dose)	1.52 ± 0.34	1.48 ± 0.32	1.63 ± 0.35	1.42 ± 0.31	1.56 ± 0.33	<0.0001	<0.0001
KRU (residual renal function) (%)	2.75 ± 2.40	2.48 ± 2.19	3.13 ± 2.74	2.19 ± 1.92	2.92 ± 2.27	<0.0001	0.013
Comorbidities (%)							
AIDS	1	1	1	1	2	0.2069	0.0645
HIV	2	2	2	2	2	0.0003	<0.0001
Cancer	4	5	4	4	3	<0.0001	<0.0001
History of hypertension	79	78	78	79	79	0.0456	0.0218
Congestive heart failure	28	30	29	26	23	<0.0001	<0.0001
Atherosclerotic heart disease	21	24	22	18	16	<0.0001	<0.0001
Peripheral vascular disease	11	14	11	10	8	<0.0001	<0.0001
Cerebrovascular disease	7	9	7	7	5	<0.0001	<0.0001
Other cardiovascular disease	5	6	5	5	4	<0.0001	<0.0001
Chronic obstructive pulmonary disease	6	7	5	5	4	<0.0001	<0.0001
Non-ambulatory	3	4	2	3	2	<0.0001	<0.0001
Current smoker	5	5	4	6	5	<0.0001	0.2321
Alcohol abuse	1	1	1	2	1	<0.0001	0.6539
Drug abuse	1	1	1	2	1	<0.0001	<0.0001
Body mass index (kg/m^2)	26.6 ± 6.9	26.2 ± 6.6	26.3 ± 6.6	27.4 ± 7.6	27.2 ± 7.0	<0.0001	<0.0001
Serum levels							
Hemoglobin (g/dl)	11.99 ± 1.31	12.00 ± 1.34	12.17 ± 1.23	11.79 ± 1.36	12.00 ± 1.28	<0.0001	<0.0001
Albumin (g/dl)	3.70 ± 0.44	3.59 ± 0.48	3.79 ± 0.37	3.68 ± 0.44	3.85 ± 0.36	<0.0001	<0.0001
Creatinine (mg/dl)	8.4 ± 3.3	7.2 ± 3.0	8.7 ± 3.1	8.7 ± 3.3	10.3 ± 3.4	<0.0001	<0.0001
Bicarbonate (mg/dl)	22.2 ± 2.9	22.9 ± 2.9	21.9 ± 2.7	22.3 ± 2.9	21.2 ± 2.8	<0.0001	<0.0001
Calcium (mg/dl)	9.2 ± 0.7	9.2 ± 0.7	9.3 ± 0.7	9.1 ± 0.8	9.2 ± 0.8	<0.0001	<0.0001
Phosphorus (mg/dl)	5.6 ± 1.5	5.1 ± 1.3	5.6 ± 1.4	5.9 ± 1.5	6.5 ± 1.5	<0.0001	<0.0001
Alkaline phosphatase (U/l)	115 ± 81	113 ± 81	104 ± 73	126 ± 87	124 ± 84	<0.0001	<0.0001
Intact parathyroid hormone (pg/ml)*	234 (133, 306)	156 (91, 219)	162 (95, 222)	481 (371, 697)	496 (380, 733)	<0.0001	<0.0001
TIBC (mg/dl)	206 ± 45	201 ± 47	211 ± 42	204 ± 45	211 ± 42	<0.0001	<0.0001
Iron saturation ratio (%)	28.7 ± 11.5	27.8 ± 11.3	30.2 ± 11.7	27.7 ± 11.0	30.0 ± 11.6	<0.0001	<0.0001
Ferritin (ng/ml)*	421(197, 773)	403 (190, 754)	472 (227, 827)	378 (175, 719)	447 (207, 804)	<0.0001	<0.0001
White blood cell ($\times 10^9$/l)	7.4 ± 2.5	7.5 ± 2.6	7.5 ± 2.5	7.2 ± 2.4	7.2 ± 2.2	<0.0001	<0.0001
Lymphocyte (% of total WBC)	20.7 ± 7.8	20.3 ± 7.8	20.4 ± 7.7	21.3 ± 8.0	21.3 ± 7.7	<0.0001	<0.0001
Protein catabolic rate (g/kg/day)	0.94 ± 0.23	0.78 ± 0.14	1.17 ± 0.13	0.81 ± 0.13	1.17 ± 0.13	<0.0001	<0.0001

Abbreviations: ANOVA, analysis of variance; KRU, renal urea clearance indicating residual renal function; Kt/*V*, dialysis dose; REG, linear regression; TIBC, total iron-binding capacity.

All values are presented as mean ± s.d. or percentages, except for asterisk (*) where values are presented as median and interquartile range.

P-values for ANOVA column are based on ANOVA or chi square test where indicated, except for asterisk (*) where it is based on Wilcoxon rank-sum test.

P-values for REG column are based on linear regression models.

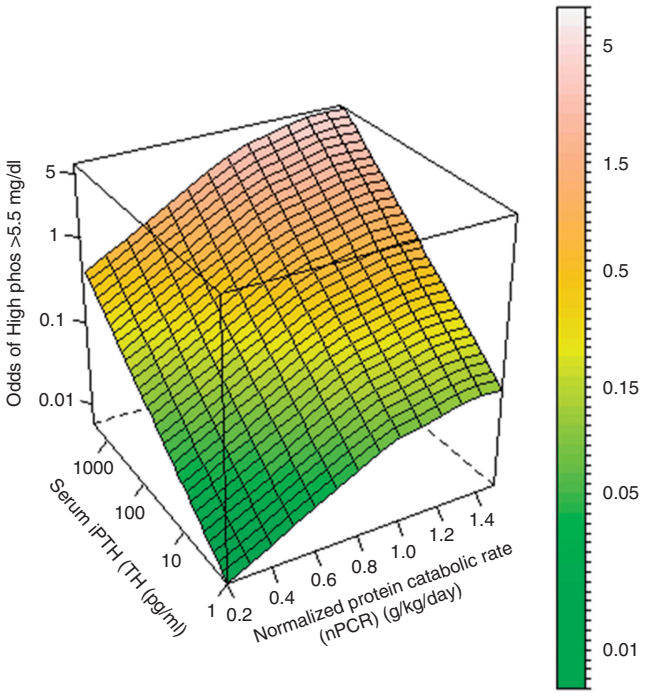

Figure 2 | Relationship between the dependent variable, log odds ratio of serum phosphorus >5.5 g/dl and independent variables, serum intact parathyroid hormone (iPTH), and normalized protein catabolic rate (nPCR).

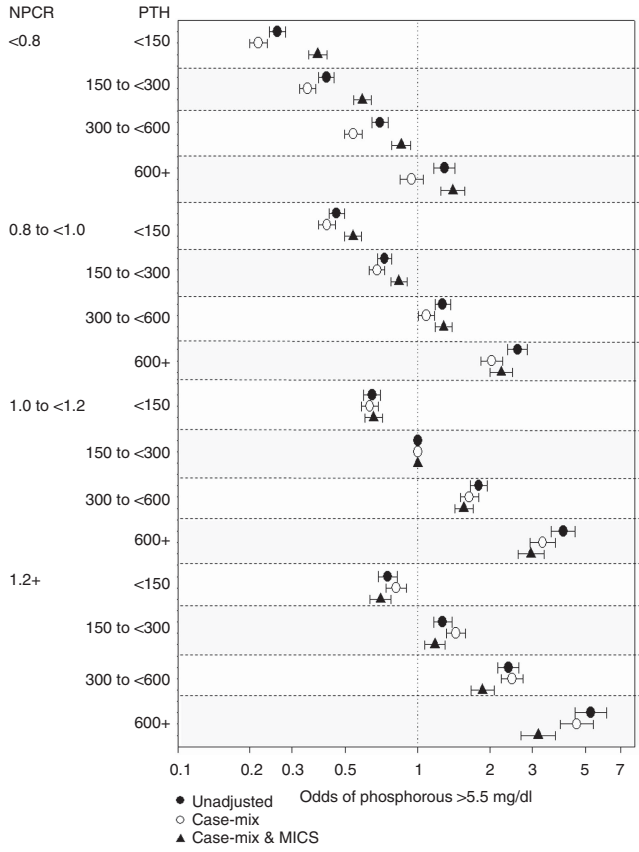

Figure 3 | Association of hyperphosphatemia with levels of serum intact parathyroid hormone (iPTH) and normalized protein catabolic rate (nPCR) in unadjusted, case-mix, and case-mix and malnutrition-inflammation cachexia syndrome (MICS) adjusted models. Serum iPTH and nPCR were each cut into four *a priori* groups resulting in $4 \times 4 = 16$ groups. Reference group is patients with iPTH level 150–<300 pg/ml and nPCR level 1.0–<1.2 g/kg/day. See text for the list of covariates in multivariate adjustment.

<0.8 g/kg/day with PTH levels <150 pg/ml had the lowest odds of associated hyperphosphatemia, whereas nPCR≥ 1.2 g/kg/day with PTH levels ≥600 pg/ml correlated with the highest risk of hyperphosphatemia. These correlations remained significant after adjustment for a variety of demographic, comorbid, and inflammation-malnutrition factors.

Our data emphasizes the interplay between dietary protein intake, PTH levels, and serum phosphorus. However, the study was not designed to define therapeutic targets for these parameters, and hard clinical outcomes such as mortality were not analyzed. We are by no means advocating for low-end nPCR and PTH levels as management strategies for hyperphosphatemia. Indeed, restricting protein intake has been associated with increased risk of death in CKD,[4,31] and MHD patients, with nPCR levels 1.0–1.4 g/kg/day conferring best survival.[27] Protein malnutrition with serum albumin levels <3.5 g/dl is a predictor of increased mortality in incident MHD patients.[32] In terms of PTH, the phenomenon of skeletal resistance to PTH in CKD has long been recognized,[33] and several mechanisms have been proposed that are beyond the scope of this paper. Although no randomized trials have validated a target range for PTH levels, observational cohort studies have reported optimal survival in MHD patients when PTH is 150–300 pg/ml.[15,34] A combination of low serum phosphorus and low PTH levels warrants cautious interpretation, as they may actually reflect protein-energy wasting and inflammation,[15,35] known predictors of increased mortality.[36]

Although the contribution of higher nPCR to increases in serum phosphorus may seem intuitive, adequate protein nutrition is important in MHD patients to avoid increased mortality.[32] Information on the phosphorus/protein ratio in various foods should be a mainstay of low-phosphate diet education; for example, egg whites are an excellent source of protein and have a very low phosphorus-to-protein content.[37] The mechanisms by which secondary hyperparathyroidism may contribute to hyperphosphatemia are less clear. The phosphaturic effects of PTH become irrelevant in the MHD population who are functionally anephric; thus hyperphosphatemia can and is likely to occur in a closed system. Secondary hyperparathyroidism induces hyperphosphatemia largely due to increased phosphorus efflux from bone. In the study by Wesseling-Perry *et al.*,[30] rise in serum phosphorus following PTH infusion in MHD patients was independent of osteodystrophy type (normal/adynamic vs. high turnover) on bone biopsy, suggesting additional extra-skeletal effects of elevated PTH on serum phosphorus. Regardless, there is a strong evidence that lowering of serum

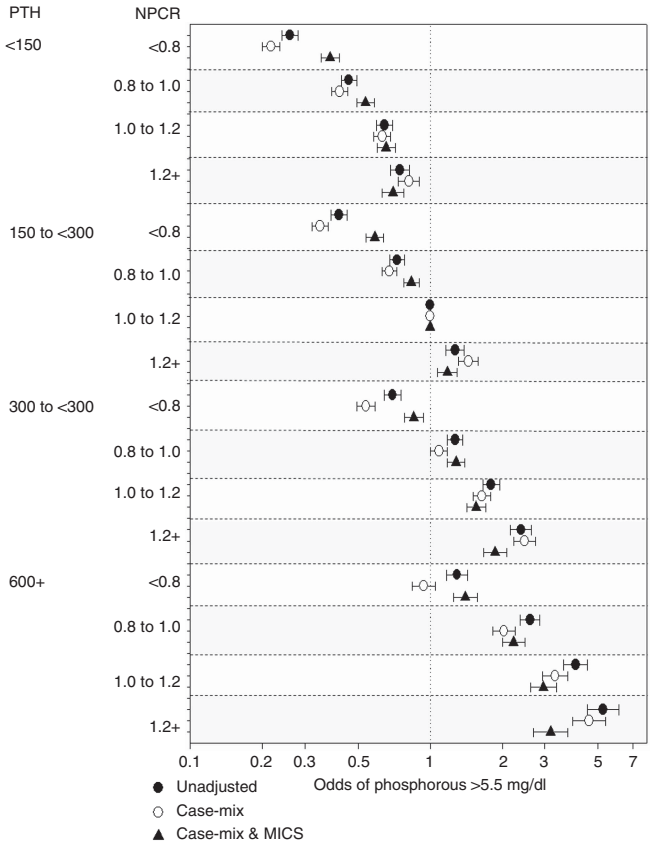

Figure 4 | Association of hyperphosphatemia with levels of normalized protein catabolic rate (nPCR) in serum intact parathyroid hormone (iPTH) groups in unadjusted, case-mix, and case-mix and malnutrition-inflammation cachexia syndrome (MICS) adjusted models. Serum iPTH and nPCR were each cut into four *a priori* groups resulting in $4 \times 4 = 16$ groups. Reference group is patients with iPTH level 150–<300 pg/ml and nPCR level 1.0–<1.2 g/kg/day. See text for the list of covariates in multivariate adjustment.

PTH is associated with lowering of serum phosphorus. Trials using the calcimimetic cinacalcet have attributed serum phosphorus reduction to lowering of PTH.[29,38] Furthermore, in a Japanese cohort of 15 MHD patients with advanced secondary hyperparathyroidism, serum phosphorus and FGF23 levels declined significantly following total parathyroidectomy.[39]

The strength of our study lies in the large number of patients, which made it possible to analyze serum phosphorus associations based on 16 groups (4 nPCR × 4 iPTH groups) with extensive adjustments for other demographic and nutritional covariates. However, our study has also some limitations. First, data for active vitamin D analogs and phosphate binder treatment were not included in the models. Lack of these data could have biased analysis of iPTH and phosphorus associations. Second, there were no data for residual renal function. Although dialysis duration may be correlated with residual renal function and was adjusted in our model, residual confounding could not be completely excluded. Third, information for comorbid conditions was obtained at the time of initiation of dialysis therapy, 3–22 months before the entry into cohort. Lastly, this is an observational study, hence we cannot determine the direction of effect from detected associations. As discussed above, there is good evidence that PTH elevation can increase serum phosphorus; however, the reverse is also true, whereby dietary phosphate loading has been shown to stimulate PTH secretion in both healthy and CKD rodents.[40,41]

In conclusion, the combination of nPCR and PTH levels served as a robust 'bivariate' predictor of hyperphosphatemia. Secondary hyperparathyroidism is an under-recognized potential mediator of elevated serum phosphorus. Patient education on the phosphorus/protein ratio in foods is warranted when promoting compliance with a low phosphorus diet. Management of hyperphosphatemia may be more effective with diligent treatment of secondary hyperparathyroidism while maintaining adequate protein intake to optimize survival.

Table 2 | Predicted serum phosphorus for a White male non-diabetic patient aged 60 years, with given nPCR and iPTH values in unadjusted, case-mix, and case-mix and MICS fully adjusted models

	nPCR	PTH	Predicted serum phosphorous—-unadjusted	Predicted serum phosphorous—case-mix	Predicted serum phosphorous—fully adjusted
Pt1	0.7	70	4.85	5.03	5.18
Pt2	0.7	250	5.12	5.25	5.36
Pt3	0.7	450	5.42	5.50	5.57
Pt4	0.7	1200	6.55	6.45	6.34
Pt5	1.1	70	5.47	5.74	5.51
Pt6	1.1	250	5.74	5.96	5.70
Pt7	1.1	450	6.04	6.21	5.90
Pt8	1.1	1200	7.17	7.16	6.68
Pt9	1.4	70	5.93	6.27	5.76
Pt10	1.4	250	6.20	6.50	5.95
Pt11	1.4	450	6.50	6.75	6.15
Pt12	1.4	1200	7.63	7.69	6.93

Abbreviations: iPTH, intact parathyroid hormone; MICS, malnutrition-inflammation cachexia syndrome; nPCR, normalized protein catabolic rate.

METHODS

Patients

We retrospectively examined data from all patients receiving HD treatment in one of the DaVita outpatient dialysis facilities during an entry period from 1 July 2001 to 30 June 2006 (i.e., for 20 consecutive calendar quarters). Inclusion criteria were patients age 18 years or older who had been undergoing dialysis for at least 90 days, were being treated with MHD at the time of entry into the cohort and had serum phosphorus, intact PTH (iPTH), and nPCR measurements at the baseline quarter. The study was approved by the Harbor-UCLA Medical Center Institutional Review Board with exemption of the requirement for a written consent form. The study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research. Given the large sample size, anonymity of the patients studied, and nonintrusive nature of the research, requirement for consent was exempted.

Demographic and clinical measures

The creation and analyses of this 5-year, non-concurrent, dynamic cohort of hemodialysis patients have been described previously.[42,43]

The first (baseline) quarter for each patient was the calendar quarter in which the patient's vintage was longer than 90 days. Data from the DaVita were merged with data from the US Renal Data System (USRDS) Medical Evidence Form 2728. Information for race/ethnicity, marital status, insurance, and coexisting conditions was obtained from the USRDS. The following 15 coexisting conditions were considered: diabetes mellitus, hypertension, atherosclerotic disease, other cardiac disease (pericarditis and cardiac arrhythmia), congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, non-ambulatory state, HIV antibody positive status, AIDS, and current smoking, alcohol, and drug use. The presence of diabetes mellitus was ascertained using data from DaVita as well. Information for comorbidities was collected at the start of dialysis but could not be updated during the study period. Dialysis vintage was defined as the time between the first day of dialysis treatment and the first day of patient cohort entry.

Laboratory values

Most blood samples were collected pre-dialysis with the exception of the post-dialysis serum urea nitrogen, which was obtained to calculate urea kinetics. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported within 24 h to a single laboratory center (DaVita Laboratory, Deland, FL), where the laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, including serum creatinine, urea, albumin, calcium, phosphorus, bicarbonate, alkaline phosphatase, and total iron-binding capacity. Serum intact PTH (first-generation immunoradiometric PTH assay, Nichols, San Juan Capistrano, CA) and ferritin was usually measured at least once during each calendar quarter. Hemoglobin was measured weekly to bi-weekly in most patients. Dialysis dose was estimated by single-pooled Kt/V using urea kinetic model. Normalized protein nitrogen appearance (nPNA or nPCR) was used as indicator of dietary protein intake. To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, that is, over a 13-week interval, were averaged. The 3-month-averaged values during the first quarter were used as baseline values.

Statistical methods

Baseline characteristics were summarized as proportions, means ($\pm$ s.d.), or medians (interquartile ranges) as dictated by data type and compared across groups of iPTH and nPCR levels (iPTH <300 with nPCR <1.0, iPTH <300 with nPCR $\geqslant 1.0$, iPTH300 with nPCR <1.0 and, iPTH300 with nPCR $\geqslant 1.0$), using analysis of variance (or Wilcoxon rank-sum test for non-parametric variables) to determine *P*-values for difference between groups and linear regression to test for trend or evaluate if there was an increasing or decreasing trend linearly across groups. We examined the possibly non-linear relation between nPCR, iPTH, and the odds ratio (OR) of hyperphosphatemia (phosphorus >5.5 mg/dl) non-parametrically with unadjusted restricted cubic splines[44]. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term with the model with the linear and cubic spline terms.

We additionally divided serum iPTH levels *a priori* into four categories (<150, 150–<300, 300–<600, and $\geqslant 600$ pg/ml) and nPCR levels into four categories (<8.0, 8.0–<1.0, 1.0–<1.2, and $\geqslant 1.2$ g/kg per day). Patients were then divided into 16 groups according to their iPTH and nPCR levels (4×4 groups). Patients with iPTH level 150–<300 pg/ml and nPCR level 1.0–<1.2 g/kg per day were considered as reference group. ORs of hyperphosphatemia were estimated by fitting multivariable logistic models with three levels of adjustment: (1) Unadjusted model that only included the main predictor variable(s) and calendar quarter of entry; (2) case-mix adjusted models that included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, comorbidities, primary insurance, marital status, delivered dialysis dose estimated by single-pool Kt/V, and residual renal function during the entry quarter, that is, urinary urea clearance; and (3) case-mix plus malnutrition-inflammation cachexia syndrome (MICS) adjusted models, which included all of the covariates in the case-mix model as well as 10 surrogates of nutritional and inflammatory status: serum albumin, calcium, creatinine, total iron-binding capacity, ferritin, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin and body mass index. Linear regression models were used to create predicted values of serum phosphorus with given levels of nPCR and serum iPTH using the same three levels of adjustment. Missing covariate data of continuous and binary variables were imputed by multiple imputation methods and a category of missing covariate data was created for each categorical variable with more than two categories. Analyses were carried out with SAS version 9.3 (SAS Institute, Cary, NC) and Stata version 10.1 (Stata Corporation, College Station, TX).

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