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.

Kidney International Supplements (2013) **3,** 462–468;
doi:10.1038/kisup.2013.96

KEYWORDS: chronic kidney disease (CKD); hemodialysis; hyperphosphatemia; parathyroid hormone; phosphorus; protein intake

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.

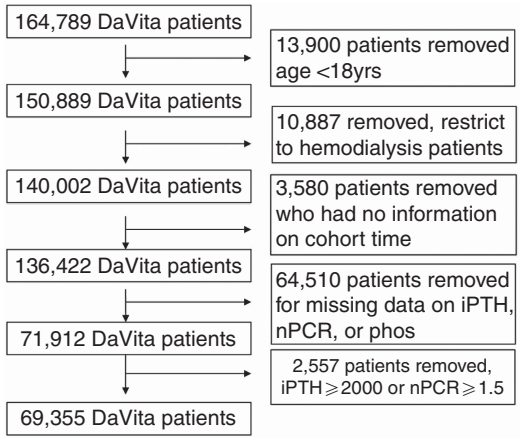

Figure 1 | Algorithm (flow chart) of patient selection for the cohort. iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; phos, phosphorus.

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