Title
Outcomes associated with serum phosphorus level in males with non-dialysis dependent chronic kidney disease.

Journal
Clinical nephrology, 73(4)

ISSN
0301-0430

Authors
Kovesdy, CP
Anderson, JE
Kalantar-Zadeh, K

Publication Date
2010-04-01

DOI
10.5414/cnp73268

Clinical Nephrology, Vol. 73 – No. 4/2010 (268-275)

ISSN 0301-0430

Outcomes associated with serum phosphorus level in males with non-dialysis dependent chronic kidney disease

C.P. Kovesdy[1,2], J.E. Anderson[3] and K. Kalantar-Zadeh[4,5]

[1]Division of Nephrology, Salem Veterans Affairs Medical Center, Salem, [2]Department of Medicine, University of Virginia, Charlottesville, VA, [3]Department of Nephrology, Johns Hopkins Bayview Medical Center, Baltimore, MD, [4]Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance and [5]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Key words
chronic kidney disease – glomerular filtration rate – mortality – phosphorus

Abstract. Background/Aims: Hyperphosphatemia is associated with higher mortality and increased incidence of end-stage renal disease in patients with non-dialysis dependent CKD (NDD-CKD), but there has not been a concomitant assessment of mortality and progressive kidney disease that would also account for cumulative effects of hyperphosphatemia. Methods: In order to account for the cumulative effects of abnormal serum phosphorus we examined associations of not only baseline, but also time-averaged serum phosphorus levels with all-cause mortality, the composite of mortality or ESRD and the slopes of estimated glomerular filtration rate (eGFR), by using Cox models and mixed effects models in a contemporary cohort of 713 males with moderate and advanced NDD-CKD. Results: Higher baseline and time-averaged serum phosphorus were both associated with mortality and with the composite outcome. A 1 mg/dl higher time-averaged serum phosphorus was associated with a multivariable adjusted hazard ratio of all-cause mortality (95% CI) of 1.56 (1.19 – 2.05), p = 0.001. Higher serum phosphorus was associated with a steeper slope of eGFR in unadjusted analyses, but this association became non-significant after multivariable adjustments. Conclusion: The cumulative burden of hyperphosphatemia is associated with increased mortality in patients with moderate and advanced NDD-CKD. Clinical trials are needed to determine if lowering serum phosphorus can result in improved mortality in this population.

Received
April 25, 2009;
accepted in revised form
October 1, 2009

Correspondence to
C. P. Kovesdy, MD
FASN
Division of Nephrology,
Salem VA Medical
Center, 1970 Roanoke
Blvd., Salem,
VA 24153, USA
csaba.kovesdy@va.gov

Introduction

Disorders of phosphorus metabolism have been implicated as a novel risk factor in the high mortality seen in patients with chronic kidney disease (CKD), including those on maintenance hemodialysis (MHD) therapy [1, 2] and also patients with non-dialysis dependent CKD (NDD-CKD) [3, 4]. In NDD-CKD higher serum phosphorus has also been associated with an increase in the incidence of end-stage renal disease [4, 5, 6], raising the possibility that hyperphosphatemia could also have distinct adverse effects on kidney function [7, 8]. The association between serum phosphorus and the incidence of ESRD could, however, be also explained by mechanisms unrelated to progressive CKD, such as censoring of patients who died before potentially reaching ESRD in Cox models [9]. Furthermore, previous studies in NDD-CKD have used baseline serum phosphorus to study outcomes, thus not accounting for the cumulative impact of changing phosphorus levels over time or for the possible effects of various medications applied in the context of such changes. In order to address these issues we examined outcomes associated not only with baseline but also with time-averaged serum phosphorus in a contemporary cohort of male patients with moderate and advanced NDD-CKD. We examined concomitantly associations with all-cause mortality, the composite of pre-dialysis mortality or ESRD, and with slopes of estimated glomerular filtration rate (eGFR).

Methods

Study population and data collection

We studied 766 patients evaluated for NDD-CKD at Salem Veterans Affairs Medical Center (VAMC) between January 1, 2001,

and June 30, 2007, and followed until April 1, 2008. 41 patients had no serum phosphorus measurements; 8 female patients and 4 patients whose race was other than white or black were also excluded. The final study population consisted of 713 men.

Baseline characteristics of the study population were collected retrospectively as recorded for clinical purposes at the time of the patients' initial evaluation in the Nephrology clinic and subsequently during the follow-up period by averaging values every 6 months if appropriate, and included demographic and anthropometric characteristics, comorbid conditions and laboratory results, as detailed before [10, 11]. Medication use, including that of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB), statins, calcium and non-calcium containing phosphate binders and calcitriol, was also assessed over the entire follow-up period by reviewing pharmacy records, and was used as a surrogate marker for quality of clinical care. Serum creatinine levels measured during outpatient visits were collected throughout the follow-up period until the occurrence of death, initiation of dialysis or loss of follow-up (whichever occurred first) for slope assessment. Glomerular filtration rate was estimated using the abbreviated equation developed for the Modification of Diet in Renal Disease Study (MDRD) [12] and categorized according to the staging system introduced by the Kidney/Dialysis Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification [13]. All the biochemical measurements were performed in a single laboratory at the Salem VAMC.

Statistical analyses

Descriptive analyses were performed and comparisons of variables between categories of serum phosphorus was done using ANOVA and χ^2-tests. Skewed variables were log-transformed. Missing data points for the Charlson comorbidity index (< 1% missing), serum albumin (< 1% missing), hemoglobin (< 1% missing) and 24-h urine protein (4% missing) were imputed by linear regression and using all other characteristics as independent variables. Serum parathyroid hormone (PTH) level was missing in 43% of patients at baseline and in 16% of patients throughout the entire follow-up. PTH level was included in multivariable analyses of baseline variables as a categorical variable by dividing baseline levels in quartiles and adding missing values as a fifth (dummy) category, and in analyses of time-averaged variables by imputing missing values. Smoking (1% missing) was analyzed as a categorical variable with the creation of a dummy variable corresponding to missing status. To better capture the cumulative impact of serum phosphorus over time we used both its baseline and time-averaged values in our analyses [14].

Outcomes analysis: The starting time for survival analysis was the date of the first encounter in the Nephrology Clinic at Salem VAMC. Patients were considered lost to follow-up if no contact was documented with them for more than 6 months, and they were censored at the date of the last documented contact. Outcome measures were overall (pre- and post-dialysis) all-cause mortality (ascertained from VA electronic records), the composite of pre-dialysis mortality or ESRD (defined as initiation of maintenance dialysis therapy and ascertained from local hospital records including Medicare Form 2728) and the slopes of estimated GFR vs. time.

The associations of baseline and time-averaged serum phosphorus levels with all-cause mortality, and the composite of pre-dialysis mortality or ESRD were evaluated in Cox models with adjustment for potential confounders. Selection of variables to be included in the final multivariable models was determined based on differences in baseline characteristics between groups with different serum phosphorus levels and based on physiologic considerations [15]. Time-averaged values of variables that were updated during follow-up were included in the multivariable models assessing associations for time-averaged serum phosphorus. Nonlinear associations were examined by using restricted cubic splines; analyses were restricted to values above the 1st and below the 99th percentile of the predictor variable in order to increase the stability of the spline models.

The association between baseline and time-averaged serum phosphorus and the slopes of eGFR vs. time was examined in gen-

Table 1. Baseline characteristics of individuals stratified by quartiles of baseline serum phosphorus level.

	Serum phosphorus (mg/dl)				p
	< 3.3 (n = 155)	3.3– < 3.8 (n = 229)	3.8– < 4.3 (n = 169)	≥ 4.3 (n = 160)	
Age (years)	69.2 ± 9.6	71.1 ± 9.6	70.3 ± 10.7	67.2 ± 10.6	0.0015
Race (black)	41 (26)	50 (22)	35 (21)	35 (22)	0.6
DM	84 (54)	125 (55)	98 (58)	107 (67)	0.07
ASCVD	90 (58)	131 (57)	95 (56)	85 (53)	0.8
Smoking	30 (19)	36 (18)	30 (18)	50 (32)	0.001
Charlson comorbidity index	2.3 ± 1.6	2.4 ± 1.5	2.5 ± 1.7	2.9 ± 1.7	0.0015
Calcitriol use	57 (37)	83 (36)	75 (47)	73 (46)	0.14
Calcium-containing medication use	17 (11)	28 (12)	24 (14)	63 (39)	< 0.001
Sevelamer HCl use	9 (6)	13 (6)	18 (11)	47 (29)	< 0.001
ACEI/ARB use	117 (75)	186 (81)	130 (77)	130 (81)	0.43
Statin use	122 (79)	175 (76)	118 (70)	128 (80)	0.13
BMI (kg/m^2)	30.0 ± 6.6	29.5 ± 5.5	29.2 ± 6.1	28.7 ± 5.9	0.22
SBP (mmHg)	142 ± 24	145 ± 25	144 ± 28	148 ± 26	0.21
DBP (mmHg)	70 ± 15	72 ± 15	70 ± 15	71 ± 14	0.6
eGFR (ml/min/1.73 m^2)	42.3 ± 13.9	38.7 ± 14.5	37.3 ± 16.8	29.3 ± 14.0	< 0.0001
Serum albumin (g/dl)	3.7 ± 0.4	3.6 ± 0.4	3.6 ± 0.5	3.4 ± 0.6	< 0.0001
Serum total cholesterol (mg/dl)	173 ± 44	176 ± 47	183 ± 49	192 ± 55	0.004
Serum calcium (mg/dl)	9.2 ± 0.5	9.3 ± 0.5	9.2 ± 0.5	9.0 ± 0.6	0.0001
Serum PTH (pg/ml)	82 (70 – 96)	88 (78 – 98)	87 (77 – 98)	116 (96 – 140)	< 0.0001
Serum bicarbonate (mEq/l)	26.0 ± 2.9	26.3 ± 3.3	26.3 ± 3.3	25.0 ± 3.7	0.0001
Blood Hgb (g/dl)	13.0 ± 1.7	13.0 ± 1.8	12.4 ± 1.9	11.9 ± 1.9	< 0.0001
Blood WBC ($1,000/mm^3$)	7.3 ± 2.3	7.5 ± 2.2	7.3 ± 1.9	7.5 ± 2.5	0.7
Blood lymphocytes (% in WBC)	22.8 ± 8.0	23.8 ± 8.9	23.6 ± 8.9	22.1 ± 8.5	0.24
Proteinuria (mg/24 h)	387 (308 – 483)	391 (333 – 455)	584 (446 – 742)	1,510 (1,211 – 1,882)	< 0.0001

Data are presented as means ± SD, number (% of total) or geometric means (95% confidence interval). DM = diabetes mellitus, ASCVD = atherosclerotic cardiovascular disease, ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, PTH = parathyroid hormone, Hgb = hemoglobin, WBC = white blood cell count. Atherosclerotic cardiovascular disease was defined as a previous history of cardiovascular, cerebrovascular or peripheral vascular disease. Comparisons are made by ANOVA or χ^2-test.

eralized linear mixed effects models allowing for a random intercept and slope using the XTMIXED command in STATA. The change in eGFR from baseline until death, start of dialysis or loss of follow-up (whichever occurred first) was studied in 645 patients who had at least 4 serum creatinine measurements (median: 14 measurements, range: 4 – 109) by using a multistage model formulation [16]. In such a model the Level 1 change describes intraindividual changes in eGFR and the Level 2 model describes how the change coefficients differ across participants. The covariates of interest (baseline and time-averaged serum phosphorus and any other independent variables) are thus included in the Level 2 model to explain interindividual differences in intraindividual change (slope).

Interactions were assessed by performing subgroup analyses by age, race, use vs. non-use of phosphate binders and calcitriol at any time during follow-up, diabetic status and by levels of kidney function, and by inclusion of interaction terms. Statistically significant interaction terms were included in the multivariable models. Sensitivity analyses were performed by using only non-imputed values of independent variables and by performing

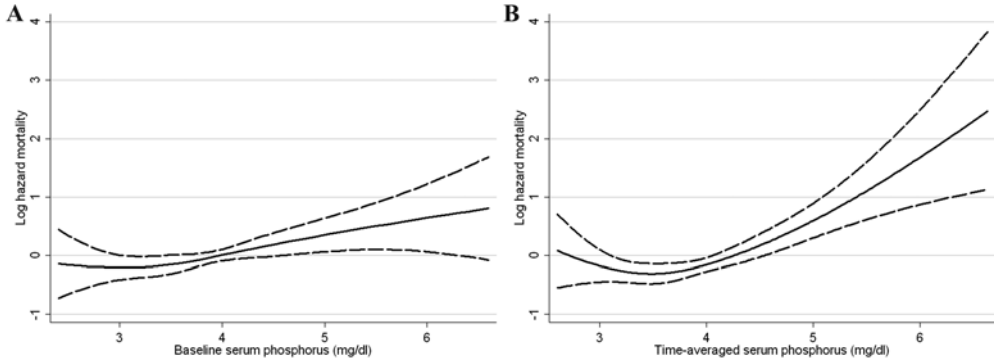

Figure 1. Multivariable adjusted log-hazards (95% confidence intervals) of all-cause mortality associated with baseline (Panel A) and time-averaged (Panel B) levels of serum phosphorus in a Cox model adjusted for baseline or (if appropriate) time-averaged age, race, smoking status, comorbidity index, diabetes mellitus, cardiovascular disease, estimated glomerular filtration rate, blood hemoglobin, serum calcium, parathyroid hormone, albumin and cholesterol, 24-hour urine protein, the use of activated vitamin D and phosphate binders throughout the entire follow-up period, and the interaction term for calcium-containing phosphate binders.

analyses without including PTH in the models. P values of less than 0.05 were considered significant. Statistical analyses were performed using STATA statistical software version 10 (STATA Corporation, College Station, TX, USA). The study protocol was approved by the Research and Development Committee at the Salem VAMC, with waiver of the need for informed consent.

Results

The mean (± SD) age of the cohort was 70 ± 10 years, 23% of patients were black and their mean estimated GFR was 37 ± 15 ml/min/1.73 m^2. Most patients had CKD Stages 3 (62%) and 4 (28%), with few patients categorized as CKD Stages 1 (1%), 2 (5%) and 5 (4%). The mean (± SD) baseline serum phosphorus was 3.9 ± 0.9 mg/dl and the mean (± SD) time-averaged serum phosphorus was 3.9 ± 0.7 mg/dl, based on a median (interquartile range) of 14 (7 – 22) serum phosphorus measurements per patient. A total of 244 patients died (mortality rate: 119/1,000 patient-years, 95% confidence interval (CI): 105 – 135), and 293 reached the composite outcome (event rate: 156/1,000 patient-years, 95% CI: 139 – 175) during a median follow-up of 1.5 years (total time at risk: 1,899 patient-years). 18 patients (2.5 %) were lost to follow-up and their characteristics were not significantly different (data not shown).

Baseline characteristics in patients divided by quartiles of serum phosphorus are shown in Table 1. Patients with higher phosphorus were younger, more likely to be diabetics and active smokers, had lower levels of eGFR, serum albumin, calcium, bicarbonate and blood hemoglobin levels and higher levels of comorbidity index, serum PTH, total cholesterol and 24-h urine protein. The use of phosphate binding medications during the entire follow-up period was more frequent in patients with higher serum phosphorus, but the use of ACEI/ARB, statins and activated vitamin D did not differ by categories of serum phosphorus level.

Higher baseline and time-averaged serum phosphorus levels were associated with linearly higher mortality rates in unadjusted Cox models, which remained significant even after adjustment for age, race, smoking status, comorbidity index, diabetes mellitus, cardiovascular disease, eGFR, serum calcium, PTH, albumin, hemoglobin, total cholesterol, 24-h urine protein, the use of phosphate binders and calcitriol and the interaction term for calcium-based phosphate binders (Figure 1) (Table 2). Higher serum phosphorus (both baseline and time-averaged) also showed a significant association with the composite outcome of pre-dialysis all-cause mortality or ESRD (Figure 2) (Table 2). Significant interactions were only present for the use of calcium-based phosphate binders, in that the association between serum phosphorus with mortality or the composite outcome was only significant in patients who did not receive such medications ((Table 2) p = 0.005 for the mortality interaction terms

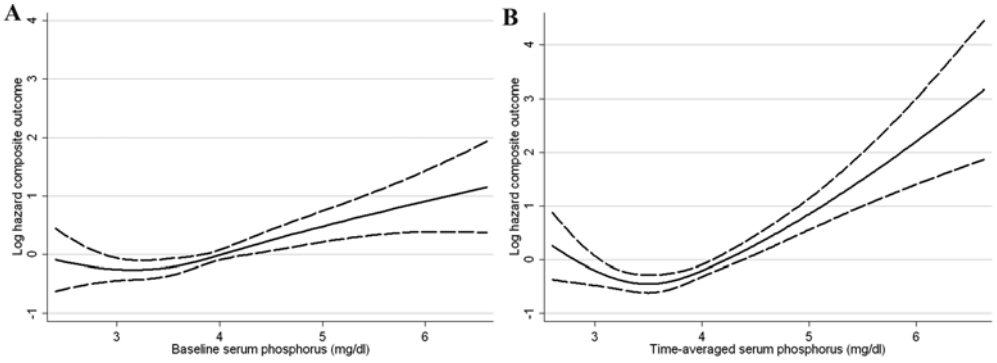

Figure 2. Multivariable adjusted log-hazards (95% confidence intervals) of the composite outcome of all-cause predialysis mortality or end-stage renal disease associated with baseline (Panel A) and time-averaged (Panel B) levels of serum phosphorus in a Cox model adjusted for baseline or (if appropriate) time-averaged age, race, smoking status, systolic and diastolic blood pressure, comorbidity index, diabetes mellitus, cardiovascular disease, estimated glomerular filtration rate, blood hemoglobin, serum calcium, parathyroid hormone, albumin and cholesterol, 24-h urine protein, the use of activated vitamin D and phosphate binders throughout the entire follow-up period, and the interaction term for calcium-containing phosphate binders.

Table 2. Unadjusted and multivariable adjusted outcomes associated with a 1 mg/dl higher serum phosphorus level.

	Mortality hazard ratio (95% CI)		Composite of mortality or ESRD hazard ratio (95% CI)		eGFR slope ml/min/1.73 m^2/year	
	Baseline PO_4	Time-averaged PO_4	Baseline PO_4	Time-averaged PO_4	Baseline PO_4	Time-averaged PO_4
Unadjusted, all	1.32 (1.14, 1.54)	1.29 (1.10, 1.50)	1.62 (1.47, 1.79)	2.00 (1.82, 2.19)	–0.83 –1.39, –0.27)	–1.42 (–2.06, –0.78)
Adjusted, all	1.31 (1.05, 1.64)	1.56 (1.19, 2.05)	1.42 (1.15, 1.76)	1.81 (1.38, 1.39)	–0.10 (–0.67, 0.47)	0.12 (–0.58, 0.81)
On calcium-containing binders, adjusted (n = 132)	1.10 (0.69, 1.77)	1.17 (0.71, 1.91)	1.01 (0.73, 1.41)	0.95 (0.65, 1.41)	0.01 (–1.13, 1.16)	–0.72 (–1.90, 0.47)
Not on calcium-containing binders, adjusted (n = 581)	1.29 (1.02, 1.63)	1.47 (1.11, 1.95)	1.45 (1.16, 1.81)	1.83 (1.38, 2.44)	–0.05 (–0.70, 0.60)	0.24 (–0.56, 1.04)

CI = confidence interval, PO_4 = serum phosphorus, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease. Mortality and the composite outcome was analyzed in Cox models. Slopes of estimated GFR were analyzed in mixed effects models. Multivariable models adjusted for age, race, comorbidity index, smoking status, systolic and diastolic blood pressure (for analyses of the composite outcome and slopes), diabetes mellitus, cardiovascular disease, estimated glomerular filtration rate, serum calcium, parathyroid hormone, hemoglobin, albumin and cholesterol, 24-h urine protein and use of calcitriol and phosphate binders.

for both baseline and time-averaged phosphorus and p = 0.03 and p = 0.01 for the composite outcome interaction terms for baseline and for time-averaged serum phosphorus).

The unadjusted mean slope of eGFR vs. time (95% CI) in the Level 1 linear mixed effects model was –1.65 ml/min/1.73 m^2/year (–2.04, –1.28), and the unadjusted mean intercept (95% CI) was 37.5 ml/min/1.73 m^2 (36.3, 38.6). Both a higher baseline and a higher time-averaged serum phosphorus were associated with significantly lower (i.e. more negative) unadjusted slopes of eGFR, but the associations became non-significant after multivariable adjustments (Table 2). In unadjusted models a serum phosphorus > 4.3 mg/dl was associated with both a lower intercept (p < 0.001 compared to serum phosphorus 3.3 – 3.8 mg/dl) (Figure 3) and a steeper slope (p < 0.001 compared to serum phosphorus 3.3 – 3.8 mg/dl) (Figure 3). In multivariable adjusted models the intercept remained significantly lower in patients with serum phosphorus > 4.3 mg/dl (p = 0.03 compared to serum phosphorus 3.3 – 3.8 mg/dl) (Figure 3), but the difference between slopes became non-significant (p = 0.3 compared to serum

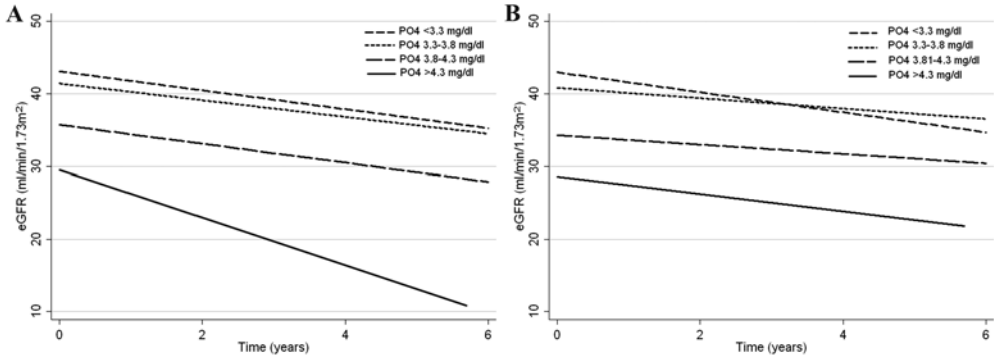

Figure 3. Unadjusted (Panel A) and multivariable adjusted (Panel B) slopes of predicted estimated glomerular filtration rates associated with different quartiles of time-averaged serum phosphorus in generalized linear mixed effects models. Multivariable models were adjusted for time-averaged age, race, smoking status, systolic and diastolic blood pressure, comorbidity index, diabetes mellitus, cardiovascular disease, baseline estimated glomerular filtration rate, blood hemoglobin, serum calcium, parathyroid hormone, albumin and cholesterol, 24-h urine protein and use of activated vitamin D and phosphate binders throughout the entire follow-up period, and interaction terms of all the above variables with time.

phosphorus 3.3 – 3.8 mg/dl) (Figure 3). Associations with baseline serum phosphorus showed similar tendencies (data not shown). The foregoing associations were similar in the various studied subgroups (Table 2).

The association of baseline and time-averaged serum phosphorus with the studied outcomes was not significantly different when including only non-imputed independent variables in multivariable models and when excluding PTH from the multivariable models (data not shown).

Discussion

We describe a significant association between higher serum phosphorus level and increased all-cause mortality in patients with moderate and advanced NDD-CKD. This association was present for baseline serum phosphorus, but was found to be even stronger when examining time-averaged serum phosphorus levels, indicating a significant cumulative effect of serum phosphorus over time. We also found a significant association between higher serum phosphorus and the composite outcome of pre-dialysis mortality or ESRD, suggesting that serum phosphorus may also be associated with worse renal outcomes. To examine if the worsened renal outcomes (i.e. increased incidence of ESRD) that we and others have described in earlier studies [4, 5, 6] is related to a more pronounced rate of loss of kidney function, we examined the intercepts and slopes of eGFR vs. time, and found that, while patients with higher serum phosphorus had lower intercepts (i.e. baseline eGFR levels), the slopes of eGFR vs. time (i.e. the rate of loss of kidney function) were not significantly different once accounting for differences in the levels of confounders.

Higher serum phosphorus has been associated with increased mortality in dialysis patients [1, 2] and in patients with NDD-CKD [3, 4, 8]. All the foregoing studies have examined baseline serum phosphorus, and could thus not account for the effects of temporal changes in the level of serum phosphorus that could be expected as eGFR declines with progressive CKD [17]. Our results support the findings of previous studies, and emphasize the importance of the cumulative impact of elevated serum phosphorus. Our findings of a significant effect modification by the administration of calcium-containing phosphate binders underscores the potentially important impact on phosphorus' association with clinical outcomes by such agents, which could alter the effects of elevated serum phosphorus not only through a phosphorus-lowering effect, but also by impacting on other homeostatic mechanisms such as PTH level, urinary phosphorus or serum fibroblast growth factor-23 (FGF-23), and also by the potentially deleterious effects of calcium loading [8, 18].

The putative mechanism(s) responsible for the observed higher mortality could be phosphorus' calcification-inducing effects in the vascular bed [19, 20], or the concomitant deleterious effects of other factors linked to hyperphosphatemia, such as secondary hyper-

parathyroidism [2, 21]. Clinical trials of phosphorus-lowering are needed to prove a causal link between higher serum phosphorus and increased mortality, but such trials have not yet been performed. A small randomized controlled trial of two different phosphate binders vs. dietary phosphate restriction in patients with NDD-CKD showed the highest progression of coronary calcification in the group treated with dietary restriction alone [18]. Serum phosphorus levels were, however, comparable in the different intervention arms of that study, thus not making it possible to support the direct role of higher phosphorus in coronary calcification.

An important additional outcome in NDD-CKD is progression of CKD, and the consequent incidence of ESRD. Prior observational studies have described an association between higher serum phosphorus and an increased incidence of ESRD [5, 6]. A higher incidence of ESRD could be the result of a more pronounced loss of kidney function, but it could also be explained by an initial lower level of kidney function (lower intercept) or by the competing nature between the endpoints of mortality and ESRD; thus it has been recommended that observational studies assessing progression of CKD examine the rate of change in kidney function rather than a fixed end-point such as ESRD [9]. Prior to ours there has been a single other study that examined the association between serum phosphorus and the rate of change in kidney function, which described an association between higher serum phosphorus levels and steeper slopes of eGFR [4]. This study included a relatively smaller number of patients with advanced (Stages 4 and 5) NDD-CKD and it may be difficult to extrapolate its findings to patients with earlier stages of CKD. Furthermore, the methodology this study applied (using ordinary least-squares slopes of eGFR) is not considered ideal for the stated purpose [16]. Our study applied a more appropriate methodology (generalized linear mixed effects models) in a robust dataset with a median of 14 eGFR values per participant. We found that the higher incidence of ESRD associated with elevated serum phosphorus that was previously reported by us and others [5, 6] could have been the result of a significantly lower intercept (i.e. a lower baseline or initial eGFR), but not necessarily a steeper slope of eGFR. This could possibly be due to a higher serum phosphorus causing more substantial loss of kidney function in earlier stages of CKD.

Our study should be qualified for several potential limitations. The historical and observational nature of the study only allows us to establish associations, but not causal relationships. Our study was limited to male patients from a single institution; hence our results may not apply to the larger population with NDD-CKD. We hypothesizes that the mortality effect of higher serum phosphorus is related to an increase in cardiovascular complications but we did not have causes of death available for analysis to substantiate this. We used estimated GFR as a measure of kidney function, and imprecision related to this method may have affected our results. Undetected unequal medical care could be responsible for differences in outcomes in retrospective studies such as ours, especially since we detected a significant interaction with calcium-based phosphate binders which were used more often in patients with elevated serum phosphorus. It is less likely though, that the more frequent use of such medications was a marker of unequal care, as other commonly used medications were applied with equal frequency in our cohort, and a better medical care signaled by more frequent use of a certain medication in the higher serum phosphorus group should have biased our results toward the null.

Conclusions

Higher serum phosphorus is associated with higher death risk in individuals with moderate and advanced NDD-CKD, but its association with an increased rate of loss of kidney function could not be substantiated. Time-averaged serum phosphorus displays a more robust association with mortality than baseline serum phosphorus, suggesting an important role for the cumulative burden of hyperphosphatemia. Based on our results one could hypothesize that long term phosphorus control could result in improved clinical outcomes in patients with moderate and advanced NDD-CKD. Clinical trials will be necessary to test such a hypothesis.

Acknowledgment

This study is supported by an investigator-initiated grant from Shire Development, Inc. to CPK (without salary support) and by grant 1R01DK078106-01 to CPK and KKZ.

Disclosure

CPK and KKZ have received grant support and/or honoraria from Fresenius, Genzyme and Shire.

References

[1] *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:* 2208-2218.

[2] *Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006; *70:* 771-780.

[3] *Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL.* Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005; *16:* 520-528.

[4] *Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, Manen JG, Boeschoten EW, Huisman RM, Krediet RT, Dekker FW.* High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007; *22:* 2909-2916.

[5] *Norris KC, Greene T, Kopple J, Lea J, Lewis J, Lipkowitz M, Miller P, Richardson A, Rostand S, Wang X, Appel LJ.* Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease. J Am Soc Nephrol. 2006; *17:* 2928-2936.

[6] *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:* 825-831.

[7] *Ritz E, Gross ML, Dikow R.* Role of calcium-phosphorous disorders in the progression of renal failure. Kidney Int. 2005; *68 (Suppl 99)*: 66-70.

[8] *Kovesdy CP, Kalantar-Zadeh K.* Bone and mineral disorders in pre-dialysis CKD. Int Urol Nephrol. 2008; *40:* 427-440.

[9] *Hsu CY, Chertow GM, Curhan GC.* Methodological issues in studying the epidemiology of mild to moderate chronic renal insufficiency. Kidney Int. 2002; *61:* 1567-1576.

[10] *Kovesdy CP, Trivedi BK, Anderson JE.* Association of kidney function with mortality in patients with chronic kidney disease not yet on dialysis: a historical prospective cohort study. Adv Chronic Kidney Dis. 2006; *13:* 183-188.

[11] *Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE.* Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. Nephrol Dial Transplant. 2006; *21:* 1257-1262.

[12] *Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D.* A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med. 1999; *130:* 461-470.

[13] *K/DOQI.* Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; *39:* 1-266.

[14] *Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE.* Association of anemia with outcomes in men with moderate and severe chronic kidney disease. Kidney Int. 2006; *69:* 560-564.

[15] *Thadhani R, Tonelli M.* Cohort studies: marching forward. Clin J Am Soc Nephrol. 2006; *1:* 1117-1123.

[16] *Singer JD, Willett JB.* Applied Longitudinal Data Analysis. Modeling Change and Event Occurrence. Oxford: Oxford University Press, Inc.; 2003.

[17] *Yu AS.* Renal transport of calcium, magnesium and phosphate. In: Brenner BM (ed). Brenner & Rector's The Kidney, 7th ed., Philadelphia: Saunders; 2004.

[18] *Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, Russo L, Scafarto A, Andreucci VE.* The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int. 2007; *72:* 1255-1261.

[19] *Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM.* Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000; *87:* 10-17.

[20] *Chen NX, O'Neill KD, Duan D, Moe SM.* Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. Kidney Int. 2002; *62:* 1724-1731.

[21] *Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K.* Secondary hyperparathyroidism is associated with higher mortality in men with moderate to severe chronic kidney disease. Kidney Int. 2008; *73:* 1296-1302.