Serum Phosphate Levels and Mortality Risk among People with Chronic Kidney Disease

Bryan Kestenbaum,* Joshua N. Sampson,† Kyle D. Rudser,† Donald J. Patterson,‡ Stephen L. Seliger,§ Bessie Young,‖¶ Donald J. Sherrard,* and Dennis L. Andress*

**Division of Nephrology, University of Washington, Veterans' Affairs Puget Sound Health Care System; Departments of †Biostatistics and ‡Computer Science and Engineering, and §Division of Nephrology, University of Washington; ‖Division of General Internal Medicine, University of Washington, Veterans' Affairs Puget Sound Health Care System; and ¶Northwest Kidney Centers, Seattle, Washington*

Elevated serum phosphate levels have been linked with vascular calcification and mortality among dialysis patients. The relationship between phosphate and mortality has not been explored among patients with chronic kidney disease (CKD). A retrospective cohort study was conducted from eight Veterans Affairs' Medical Centers located in the Pacific Northwest. CKD was defined by two continuously abnormal outpatient serum creatinine measurements at least 6 mo apart between 1999 and 2002. Patients who received chronic dialysis, those with a present or previous renal transplant, and those without a recent phosphate measurement were excluded. The primary end point was all-cause mortality. Secondary end points were acute myocardial infarction and the combined end point of myocardial infarction plus death. A total of 95,619 veterans with at least one primary care or internal medicine clinic contact from a Northwest VA facility and two or more outpatient measurements of serum creatinine, at least 6 mo apart, between January 1, 1999, and December 31, 2002, were identified. From this eligible population, 7021 patients met our definition of CKD. After exclusions, 6730 CKD patients were available for analysis, and 3490 had a serum phosphate measurement during the previous 18 mo. After adjustment, serum phosphate levels >3.5 mg/dl were associated with a significantly increased risk for death. Mortality risk increased linearly with each subsequent 0.5-mg/dl increase in serum phosphate levels. Elevated serum phosphate levels were independently associated with increased mortality risk among this population of patients with CKD.

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Phosphate excess has been implicated in the substantial cardiovascular morbidity and mortality observed among people who receive chronic dialysis (1). Hyperphosphatemia has been independently linked with calcification of the coronary arteries and aorta (2,3), as well as cardiovascular and all-cause mortality in the setting of ESRD (1,4,5). Control of hyperphosphatemia is an integral component of the routine care of chronic dialysis patients (6).

The relationship between serum phosphate levels and mortality risk has not been explored among nondialysis patients with chronic kidney disease (CKD). A decline in renal function leads to phosphate retention, elevated parathyroid hormone (PTH) levels, and low 1,25-dihydroxy vitamin D levels; however, serum phosphate levels are often maintained within the normal laboratory range until relatively late in the course of CKD (7–9). *In vitro*, smooth muscle cells express osteogenic markers and mineralize in the presence of inorganic phosphate concentrations that are similar to those found among people with CKD (10). The abundance of atherosclerotic risk factors that are coincident with chronic renal disease, including diabetes, dyslipidemia, microinflammation, and hyperhomocysteinemia (11), may create a synergistic environment for phosphate to exert toxic vascular effects.

Given the strong link between phosphate levels and mortality among chronic dialysis patients, we hypothesized that higher serum phosphate levels would be associated with increased mortality risk among people with CKD. To address this hypothesis, we studied a cohort of U.S. veterans with CKD from the Pacific Northwest.

Materials and Methods

Data Source

Data were abstracted from the Veterans' Affairs (VA) Consumer Health Information and Performance Sets (CHIPS) data system. CHIPS acquires patient information directly from the VA Information Systems and Technology Architecture (VISTA), the computerized medical record system used throughout the VA system. VISTA maintains patient-level data, including demographics, pharmacy records, laboratory measurements, diagnosis and procedure codes, and vital signs for all outpatient and inpatient VA patient encounters. Additional dialysis and transplantation information was obtained by linking the patient cohort to the United States Renal Data System (USRDS).

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Address correspondence to: Dr. Bryan Kestenbaum, Veterans' Affairs Puget Sound Health Care System, Division of Nephrology, Mail Stop 111A, 1660 South Columbian Way, Seattle, WA 98108. Phone: 206-277-3192; Fax: 206-764-2022; E-mail: brk@u.washington.edu

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Patient Population

The source population consisted of veterans with at least one outpatient primary care or internal medicine subspecialty clinic visit within the Northwest Veterans Integrated Service Network (VISN 20), a collection of eight VA facilities located in Washington State, Idaho, Oregon, and Alaska. From this population, a cohort of patients with CKD was identified. CKD was defined by two abnormal outpatient serum creatinine measurements at least 6 mo but no more than 2 yr apart, without normal intervening creatinine measurements. Abnormal creatinine measurements were defined as ≥1.2 mg/dl (106.1 μmol/L) for women and ≥1.5 mg/dl (132.6 μmol/L) for men (12). Creatinine measurements were screened between January 1, 1999, and December 31, 2002. The date of the second abnormal outpatient creatinine measurement that defined each study patient as having CKD served as their study start date.

Patients with a present or past history of chronic dialysis or renal transplantation were excluded from analysis. Furthermore, patients without a serum phosphate measurement during the 18-mo period before their study start date (the baseline period) were excluded. Dialysis and transplantation status was ascertained by linking USRDS data to the CHIPS database via unique patient identifiers.

Data Collection

Time-weighted averages for each laboratory measurement and vital sign of interest were calculated during the 18-mo baseline period. Time-weighted averaging was chosen to provide the most accurate reflection of the mean of each characteristic during the baseline period and to minimize the potential problem of overweighing multiple measurements that might occur during a short period, such as a hospitalization or period of frequent outpatient contact. The time-weighted average was calculated by weighing each measurement by the time span contributed until subsequent measurement. Laboratory measurements of interest were creatinine, calcium, albumin, LDL, HDL, triglycerides, bicarbonate, and hemoglobin. The specific serum creatinine level at the study start date was also studied. Vital signs of interest were systolic and diastolic BP, height, and weight.

Prevalent comorbid medical conditions were defined by examining all available data from the initiation of VISTA (January 1985) until the study start date. Diabetes was defined by at least one of the following: (*1*) two outpatient or one inpatient *International Classification of Diseases, Ninth Revision—Clinical Modification* (ICD-9-CM) code for diabetes; (*2*) a prescription for insulin, glucose test strips, a glucometer, or an oral hypoglycemic medication; (*3*) any hemoglobin A_{1C} >7.0; or 4) two or more random glucose measurements >200 mg/dl (11.1 mmol/L). Ischemic heart disease was defined by previous ICD-9-CM diagnosis codes for ischemic heart disease or a previous ICD-9-CM procedure code for coronary angioplasty or coronary artery bypass grafting. Cerebrovascular disease was defined by previous ICD-9-CM diagnosis codes for stroke or a previous ICD-9-CM procedure code for carotid endarterectomy. Congestive heart failure (CHF) was defined by previous ICD-9-CM codes for congestive heart failure. Acute renal failure (ARF) was defined by inpatient ICD-9-CM codes for acute renal failure or an inpatient ICD-9-CM procedure code for hemodialysis during the baseline period. Patients without a specific ICD-9 code diagnosis for each condition were considered not to have that condition.

Oral medications of interest included the use of statins, angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin II receptor antagonists, calcium, calcitriol, and vitamin D2 or D3 products. Baseline medication use was presumed when there was an active, filled prescription within 30 d of the study start date. Total elemental calcium intake from medications during the baseline period was calculated by multiplying the calcium content of each medication by the number of pills dispensed. The creatinine clearance (CrCl) was estimated using the method of Cockcroft and Gault (13), which was found recently to compare favorably to the abbreviated Modification of Diet in Renal Disease (MDRD) formula among older, white individuals (14). Patients were classified by CKD stage using calculated CrCl (15).

Ascertainment of Exposure

The time-weighted mean serum phosphate concentration during the baseline period was the exposure of interest. Phosphate measurements recorded during hospitalizations for ARF were excluded to reduce the potential confounding influence of ARF.

Ascertainment of Outcomes

The primary outcome of interest was all-cause mortality. Secondary outcomes included hospitalized, acute myocardial infarction (MI), and the combined end point of death plus MI. Hospitalization for acute MI was defined by ICD-9-CM diagnosis codes 410.x, which have been found to be sensitive and specific for the diagnosis of acute MI (16). No information regarding cause of death is currently available through CHIPS; therefore, cardiovascular-specific death could not be analyzed.

Statistical Analyses

All patients were followed from their study start date until they incurred the outcome of interest, reached ESRD, or were lost to follow-up or the study closed on January 31, 2004. ESRD status was determined via linked USRDS data. Specific dialysis start dates are not yet available for patients who initiated dialysis in 2003; thus, these patients were censored on January 1, 2003. Loss to follow-up was defined as 18 consecutive months without a VA contact, in the absence of death. Patients who were found to be lost to follow-up were censored at their last contact visit with the VA. In the case when the outcome was MI only, patients were censored at the date of death.

The Cox proportional hazards model was used to estimate the independent relationship between baseline serum phosphate levels and each outcome of interest. Potential confounders that were chosen before the analyses included age, race, gender, previous medical conditions, total elemental calcium intake from medications, hemoglobin, calcium, and the baseline serum creatinine. To reduce further the potential confounding effect of renal function, we explored a second model that included time-averaged creatinine, rate of creatinine change, and the maximal value for creatinine during the baseline period. A third exploratory model added BP, body mass index, cardiovascular medications, albumin, bicarbonate, and triglycerides.

In separate models, phosphate was examined as a linear term and a flexible categorical variable in 0.5-mg/dl (0.16 mmol/L) increments. Proportional hazards models were stratified by individual VA site. Because race was not reported among 20% of the cohort, race was imputed for the multivariate models using the method described by Rubin (17). Diagnostics, including Schoenfeld residuals, were checked for violations of model assumptions.

A local smoother applied to a plot of phosphate *versus* estimated CrCl was used to estimate average phosphate levels relative to renal function and to define upper and lower quintiles for phosphate, relative to CrCl. Kaplan-Meier survival curves were plotted for three groups categorized as having low (lowest quintile), average (middle three quintiles), and high (highest quintile) phosphate levels relative to peers with similar CrCl. Statistical analyses were conducted using STATA version 8.0 (STATA Corp., College Station, TX) and S-Plus (Insightful Corp., Seattle, WA). The study was approved by the University of Washington Institutional Review Board.

Results

We identified 194,535 veterans with a primary care or internal medicine specialty clinic contact from a Northwest VA facility (VISN 20) between January 1, 1999, and December 31, 2002. Among this population, 95,619 veterans had two or more serum creatinine measurements during this period, and 7021 met the definition of CKD. We excluded 179 (2.5%) patients who were receiving chronic dialysis, 60 (0.9%) patients with a present or past history of renal transplantation, and 52 (0.7%) patients without further VA contact after the study start date. After these exclusions, 6730 patients with CKD entered the study (Table 1).

Among the CKD cohort, 67.4% of patients had stage III CKD, with a median baseline creatinine concentration of 1.7 mg/dl and a median estimated CrCl of 45.1 ml/min (interquartile range [IQR], 35.6–56.5 ml/min). Only 10.1% of the cohort was seen in a nephrology clinic during the baseline period, reflecting the distribution of the study population toward early renal insufficiency. Contact with the VA system was robust; the median number of VA outpatient contacts was 10 per year during the baseline period.

Serum phosphate levels were measured at least once during the baseline period among 3490 (51.9%) patients. Although phosphate measurements recorded during episodes of ARF were excluded, patients with at least one baseline phosphate measurement were more likely to have a history of ARF as

Table 1. Baseline characteristics of the CKD patient cohort, by serum phosphate level[a]

	% Complete	Serum Phosphate Level (mg/dl [mmol/L])			
		<2.5 (<0.81; *n* = 201)	2.5–3.499 (0.81–1.13; *n* = 1782)	3.5–4.499 (0.81–1.45; *n* = 1275)	>4.5 (>1.45; *n* = 232)
Age, mean (SD)	100%	71.8 (10.1)	72.2 (10.1)	70.7 (10.5)	65.6 (11.5)
Race, % (*n*)	81.5%				
white		75.6 (152)	72.3 (1289)	75.5 (963)	77.2 (179)
black		5.5 (11)	5.6 (99)	5.7 (73)	8.6 (20)
other		0.5 (1)	1.5 (26)	2.3 (29)	1.7 (4)
missing		18.4 (37)	20.7 (368)	16.5 (210)	12.5 (29)
Gender, % (*n*)	100%				
male		97.5 (196)	96.5 (1720)	95.3 (1215)	95.7 (222)
female		2.5 (5)	3.5 (62)	4.7 (60)	4.3 (10)
Past medical history, % (*n*)	100%				
diabetes		32.8 (66)	38.2 (680)	53.7 (685)	62.5 (145)
ischemic heart disease		60.7 (122)	58.6 (1044)	64.3 (820)	59.5 (138)
congestive heart failure		34.3 (69)	35.6 (634)	45.7 (583)	46.6 (108)
cerebrovascular disease		20.4 (41)	12.2 (218)	13.5 (172)	12.1 (28)
acute renal failure		4.5 (9)	5.3 (95)	8.5 (108)	13.4 (31)
Medication use, % (*n*)	100%				
ACE inhibitor		42.8 (86)	44.9 (800)	46.7 (595)	47.8 (111)
angiotensin II receptor blocker		9.0 (18)	8.5 (151)	9.2 (117)	13.8 (32)
statin		30.8 (62)	37.9 (676)	41.6 (530)	44.0 (102)
calcium blocker		32.8 (66)	34.7 (618)	40.2 (512)	47.8 (111)
oral calcium		8.0 (16)	8.2 (146)	12.1 (154)	25.4 (59)
Vital signs, mean (SD)					
body mass index[b]	94.2%	29.1 (5.5)	29.6 (5.7)	29.6 (6.1)	29.8 (5.9)
systolic BP (mmHg)[b]	94.8%	143.0 (18.3)	142.6 (18.8)	143.2 (20.1)	147.6 (20.5)
diastolic BP (mmHg)[b]	94.8%	76.3 (10.4)	74.2 (10.5)	73.2 (11.1)	76.5 (11.8)
Laboratory data, mean (SD)					
creatinine (μmol/L)[c]	100%	155.9 (28.6)	165.7 (43.9)	187.8 (73.2)	272.2 (154)
estimated CrCl (ml/min)[c]	94.4%	50.4 (18.5)	48.6 (17.2)	45.9 (19.2)	39.5 (18.1)
albumin (g/L)[b]	97.2%	139.3 (14.1)	134.7 (15.2)	128.2 (15.6)	122.6 (16.1)
hemoglobin (g/L)[b]	93.5%	39.0 (4.3)	38.9 (4.0)	38.3 (4.7)	37.5 (5.3)
bicarbonate (mmol/L)[b]	87.1%	26.3 (3.0)	26.1 (2.7)	25.7 (3.1)	24.6 (3.3)
calcium (mmol/L)[b]	96.0%	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)	2.3 (0.2)

[a]CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; CrCl, creatinine clearance.
[b]Time-averaged values during the 18-mo baseline period.
[c]Cockroft-Gault estimated CrCl from serum creatinine value at the study start date.

compared with patients without a baseline phosphate measurement (Table 2). The subpopulation with at least one baseline phosphate measurement also had a higher prevalence of cardiovascular disease and was more likely to be using oral calcium, as compared with patients without a baseline phosphate measurement. Other characteristics were similar comparing patients with and without baseline phosphate measurements, including estimated CrCl, body mass index, and cardiovascular medication use. Patients without a baseline serum phosphate measurement had an estimated 20% lower risk for death, as compared with patients with at least one serum phosphate measurement. Further analyses were conducted among the 3490 patients with at least one phosphate measurement during the baseline period (Table 1).

Table 2. Comparison of baseline characteristics among patients with and without a baseline phosphate measurement[a]

	Phosphate Measured during 18-Month Baseline Period	
	Yes (n = 3490)	No (n = 3240)
Age, mean (SD)	71.2 (10.4)	73.4 (9.6)
Race, % (n)		
white	74.0 (2583)	70.6 (2287)
black	5.8 (203)	4.8 (156)
other	1.7 (60)	1.4 (46)
missing	18.5 (644)	23.2 (751)
Gender, % (n)		
male	96.1 (3353)	96.4 (3122)
female	3.9 (137)	3.6 (118)
Past medical history, % (n)		
diabetes	45.2 (1576)	39.6 (1284)
ischemic heart disease	60.9 (2124)	50.6 (1639)
congestive heart failure	39.9 (1394)	26.1 (845)
cerebrovascular disease	13.2 (459)	9.5 (307)
acute renal failure	7.0 (243)	1.1 (36)
Medication use, % (n)		
ACE inhibitor	45.6 (1592)	51.2 (1660)
angiotensin II receptor blocker	9.1 (318)	7.0 (226)
statin	39.3 (1370)	38.2 (1239)
calcium blocker	37.4 (1307)	33.3 (1078)
oral calcium	10.7 (375)	5.1 (165)
Vital signs, mean (SD)		
body mass index[a]	29.6 (5.9)	29.3 (5.4)
systolic BP (mmHg)[a]	143.2 (19.4)	144.0 (19.0)
diastolic BP (mmHg)[a]	74.1 (10.8)	74.5 (10.6)
Laboratory data, mean (SD)		
creatinine (μmol/L)[b]	180.3 (72.7)	163.6 (46.7)
estimated CrCl (ml/min)[b]	47.2 (18.3)	47.5 (15.9)
albumin (g/L)[a]	38.6 (4.4)	39.4 (4)
hemoglobin (g/L)[a]	131.7 (15.9)	136.9 (15.2)
bicarbonate (mmol/L)[a]	25.8 (2.9)	26.5 (2.8)
calcium (mmol/L)[a]	2.3 (0.1)	2.3 (0.1)

[a]Time-averaged values during the 18-mo baseline period.
[b]Cockroft-Gault estimated CrCl from serum creatinine value at the study start date.

The median number of phosphate and creatinine measurements during the baseline period was 2 (IQR, 1–4) and 7 (IQR, 4–13), respectively. Fewer than 2% of the patients with phosphate measurements was prescribed calcitriol or another vitamin D preparation at the study start. Furthermore, PTH levels were measured among only 7.1% of patients. Thus, vitamin D use and PTH were not analyzed further. Patients with higher serum phosphate levels tended to be younger, with a greater prevalence of diabetes, CHF, and ARF at baseline, as compared with patients with lower phosphate levels (Table 1). Higher serum phosphate levels were also associated with lower estimated CrCl, hemoglobin, and bicarbonate levels. Triglyceride levels were higher among patients with elevated serum phosphate levels; however, no relationship between phosphate and LDL or HDL cholesterol levels was observed.

To assess the relationship between phosphate levels and renal function, we calculated estimated CrCl among 3295 (94.4%) patients who had a weight measurement during the baseline period. On average, serum phosphate levels increased marginally with declining estimated CrCl, until CrCl dropped below approximately 40 ml/min (Figure 1). At this point, the mean phosphate levels increased rapidly as CrCl decreased; however, absolute phosphate levels still generally remained within the normal range. Considerable variation in serum phosphate levels was noted among patients with similar estimated CrCl. To capture this variation, we categorized phosphate levels relative to CrCl into upper, lower, and middle three quintiles (Figure 1). These categories were subsequently used to describe survival.

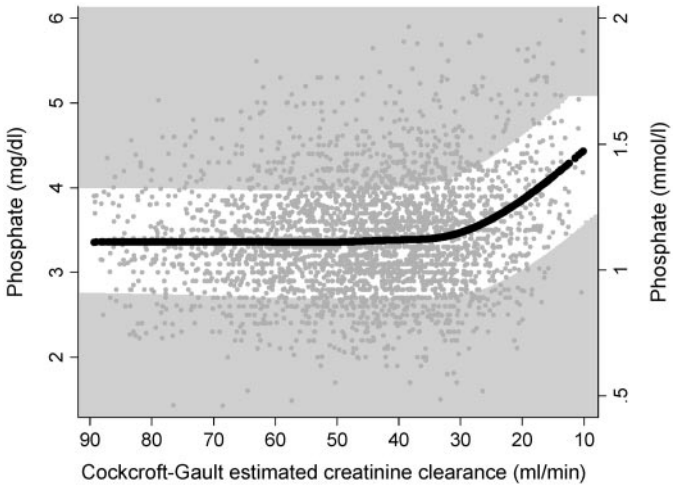

Figure 1. Mean serum phosphate levels as a function of baseline estimated creatinine clearance (CrCl). Black line represents smoothed mean serum phosphate levels relative to estimated CrCl. Gray shaded areas contain phosphate measurements that are in the highest and lowest quintiles for estimated CrCl. White area contains serum phosphate measurements within the three middle quintiles, relative to estimated creatinine clearance.

During a median follow-up of 2.1 yr, 1133 (32.5%) patients died, 257 (7.4%) reached ESRD, and 158 (4.5%) were lost to follow-up, with the remainder surviving until the study closed on January 1, 2004. The overall mortality rate was 140.8 deaths per 1000 person-years. Kaplan-Meier estimates of survival (Figure 2) were significantly different among patients with relative phosphate measurements that were in the highest or lowest quintile predicted by their estimated CrCl (log-rank test $P < 0.001$). After 3 yr of follow-up, survival was 72.2% (95% confidence interval [CI], 0.68 to 0.76) among patients in the lowest phosphate quintile, 67.3% (95% CI, 0.65 to 0.70) among patients in the middle three phosphate quintiles, and 56.4% (95% CI, 0.52 to 0.61) among patients in the highest phosphate quintile, relative to estimated CrCl.

In an unadjusted survival model, each 1-mg/dl (0.323 mmol/L) increase in serum phosphate was associated with a 44% increase in mortality risk (95% CI, 1.33 to 1.56). After adjustment for age, renal function, comorbid conditions, race, gender, hemoglobin, serum calcium, and elemental calcium intake from medications, serum phosphate remained significantly and independently related to mortality (Table 3). Each 1-mg/dl (0.323 mmol/L) increase in serum phosphate was associated with an estimated 23% increased risk for death (95% CI, 1.12 to 1.36). Further adjustment for additional measures of renal function and other covariates did not appreciably alter the association between phosphate levels and mortality. A roughly linear relationship between serum phosphate and mortality was observed when phosphate levels were examined categorically, in 0.5-mg/dl (0.16 mmol/L) increments. A statistically significant increase in mortality risk was noted with phosphate levels >3.5 mg/dl (1.13 mmol/L; Table 4). Because baseline phosphate levels were analyzed, it would be expected that the association between phosphate and mortality would diminish with time. Allowing the coefficient for phosphate to vary with time yielded an adjusted hazard ratio (HR) of 1.28 (95% CI, 1.15 to 1.43) for the first 2.5 yr of follow-up, with similar survival estimates for each year individually, and an adjusted HR of 1.13 (95% CI, 0.90 to 1.41) for years 2.5 through the end of follow-up.

Individual Cox models stratified by age, diabetic status, CHF, ARF, estimated CrCl, and serum calcium revealed elevated serum phosphate levels to be consistently associated with in-

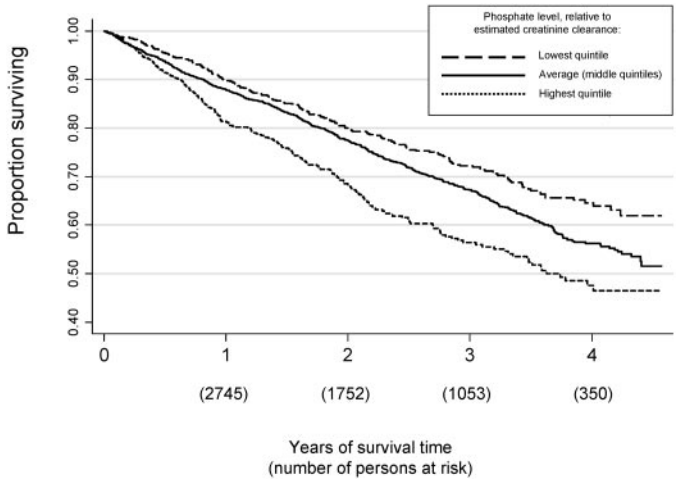

Figure 2. Kaplan-Meier survival plots by serum phosphate group, relative to estimated CrCl. The normal phosphate group refers to patients with phosphate measurements in the middle three quintiles relative to estimated CrCl (white region of Figure 1). High and low phosphate groups refer to patients with phosphate measurements in the highest and lowest quintiles relative to estimated CrCl (gray shaded regions of Figure 1).

Table 3. Multivariate Cox regression analysis results for all-cause mortality[a]

	Adjusted HR (95% CI)	*P* Value
Age (per 10-yr increase)	1.40 (1.30–1.50)	<0.001
Race		
white	Reference	
black	0.71 (0.52–0.97)	0.029
other	0.63 (0.36–1.09)	0.097
Gender		
male	Reference	
female	0.67 (0.45–1.00)	0.051
Past medical history		
diabetes	1.25 (1.10–1.42)	<0.001
ischemic heart disease	1.14 (0.98–1.32)	0.089
congestive heart failure	1.66 (1.45–1.90)	<0.001
cerebrovascular disease	1.18 (1.00–1.40)	0.044
acute renal failure	1.45 (1.19–1.78)	<0.001
Elemental calcium from prescribed medications		
none	Reference	
1–500 mg/d	1.18 (0.98, 1.43)	0.081
>500 mg/d	1.01 (0.76–1.35)	0.926
Baseline creatinine (per 1-mg/dl increase; equivalent to 88-μmol/L increase)	1.38 (1.28–1.49)	<0.001
Hemoglobin (per 0.1-g/L increase)	0.87 (0.83–0.91)	<0.001
Calcium (per 0.25-mmol/L increase)	1.02 (0.90–1.16)	0.747
Phosphate (per 1-mg/dl increase; equivalent to 0.323-mmol/L increase)	1.23 (1.12–1.36)[b]	<0.001
	1.24 (1.13–1.37)[c]	<0.001
	1.33 (1.15–1.54)[d]	<0.001

[a]HR, hazard ratio; CI, confidence interval.
[b]Adjusted for all variables listed in the table.
[c]Adjusted for all variables listed in the table plus the inverse of baseline creatinine, time-averaged creatinine (area under the curve), slope of creatinine, and maximal creatinine level during the baseline period (model 2).
[d]Adjusted for all variables in model 2 plus systolic and diastolic BP; body mass index; number of previous hospitalizations; use of an ACE inhibitor, an angiotensin II receptor antagonist, a statin, or a calcium channel blocker; and time-averaged values of albumin, bicarbonate, and triglycerides (model 3).

creased mortality risk across patient subgroups (Figure 3). Therefore, the effect of phosphate could not simply be a surrogate for these confounders. Of note, the association between elevated serum phosphate levels and mortality was not found to vary significantly by serum calcium level. We further explored multiple laboratory definitions of ARF, the most inclusive of which being a 50% rise in serum creatinine level at any time during the baseline period, which applied to 20% of the cohort. The association between serum phosphate levels and mortality was not appreciably different after excluding patients with ARF by this definition.

During follow-up, 241 acute MI occurred (31.3 MI per 1000 person-years). After adjustment for relevant confounders (model 2), each 1-unit increase in serum phosphate was associated with a significant 35% increased risk for acute MI (HR, 1.35; 95% CI, 1.09 to 1.66) and a 28% increased risk for the combined end point of death plus nonfatal MI (HR, 1.28; 95% CI, 1.16 to 1.40). These associations were found to increase in magnitude after adjustment for additional covariates (model 3).

Discussion

In this observational study, we observed associations between elevated serum phosphate levels and the risk for mortality and MI among CKD patients, independent of renal function and other known confounding factors. Surprising, the association between higher phosphate levels and mortality risk was present among patients with absolute serum phosphate levels in the high-normal range (Table 4). We did not observe an increase in mortality risk among people with lower serum phosphate levels.

The observed magnitude of association between serum phosphate levels and mortality risk was somewhat greater than that previously reported among people with ESRD (1,5). Potential explanations include our use of multiple phosphate measurements during the baseline period, which reduces misclassification, differing ranges of phosphate levels among CKD *versus* ESRD populations, and differing effects of phosphate among different patient populations.

Although this study was not designed to identify the causative role of phosphate in mortality risk, several plausible mechanisms might explain our findings. For example, cultured smooth muscle cells respond to inorganic phosphate concentrations of 1.4 mmol/L (approximately 4.3 mg/dl) by expressing bone markers core binding factor-1 and osteocalcin, with subsequent mineralization of the extracellular matrix (10). Clinically, serum phosphate levels have been associated with the presence and extent of coronary artery and aortic calcification among patients who receive chronic dialysis (2,3). Thus, it is possible that serum phosphate levels increase mortality risk by contributing to vascular calcification.

Phosphate excess may also influence mortality and cardiovascular risk by increasing circulating PTH or decreasing 1,25-dihydroxy vitamin D levels. Elevated serum phosphate levels are associated with higher PTH levels among CKD patients (9), and hyperparathyroidism is associated with cardiovascular disease in states of abnormal and normal renal function (4,18,19). Animal studies of experimental renal failure have linked PTH excess to intracellular calcium overload, cardiac fibrosis, and impaired myocardial energy production (20–22). Clinical studies of chronic dialysis patients have documented associations between PTH excess and the prevalence of left ventricular hypertrophy (23), as well as the risk for cardiovascular and all-cause mortality (4). However, the relationship between PTH and mortality varies across studies of dialysis patients (24), likely as a result of differences in the characteristics of ESRD patients with low *versus* high PTH levels. Among people without renal disease, PTH levels correlate with the extent of left ventricular hypertrophy by echocardiography (19), and epidemiologic data have documented an association between primary hyperparathyroidism and cardiovascular-specific mortality (18).

Decreased vitamin D levels may also contribute to the risk for adverse cardiovascular outcomes associated with higher phosphate levels. 1,25-Dihydroxy vitamin D levels have been inversely correlated with the extent of coronary artery calcification among individuals who are at risk for coronary disease without CKD (25). Among our study cohort, vitamin D deficiency was likely to have been present, because data from this institution have documented low serum 1,25-dihydroxy vitamin D levels among the majority of CKD patients with esti-

Table 4. Mortality rates and Cox regression results by phosphate category

Serum phosphate level		No. of Patients	Crude Mortality Rate per 1000 Person-Years (No. of Deaths)	Adjusted HR[a] (95% CI)
mg/dl	mmol/L			
<2.5	<0.81	201	101.7 (54)	0.95 (0.69–1.32)
2.5–2.999	0.81–0.9699	684	102.6 (180)	Reference
3.0–3.499	0.97–1.1299	1098	125.1 (327)	1.15 (0.95–1.39)
3.5–3.999	1.13–1.2899	887	162.7 (309)	1.32 (1.09–1.61)
4.0–4.499	1.29–1.4499	388	192.8 (144)	1.34 (1.05–1.71)
4.5–4.999	1.45–1.6199	141	256.9 (62)	1.83 (1.33–2.51)
≥5.0	≥1.62	91	304.7 (38)	1.90 (1.30–2.79)

[a]Adjusted for age, race, gender, prevalent diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, acute renal failure, calcium intake from medications, hemoglobin, serum calcium, the inverse of baseline creatinine, time-averaged creatinine (area under the curve), slope of creatinine, and maximal creatinine concentration during the baseline period (model 2).

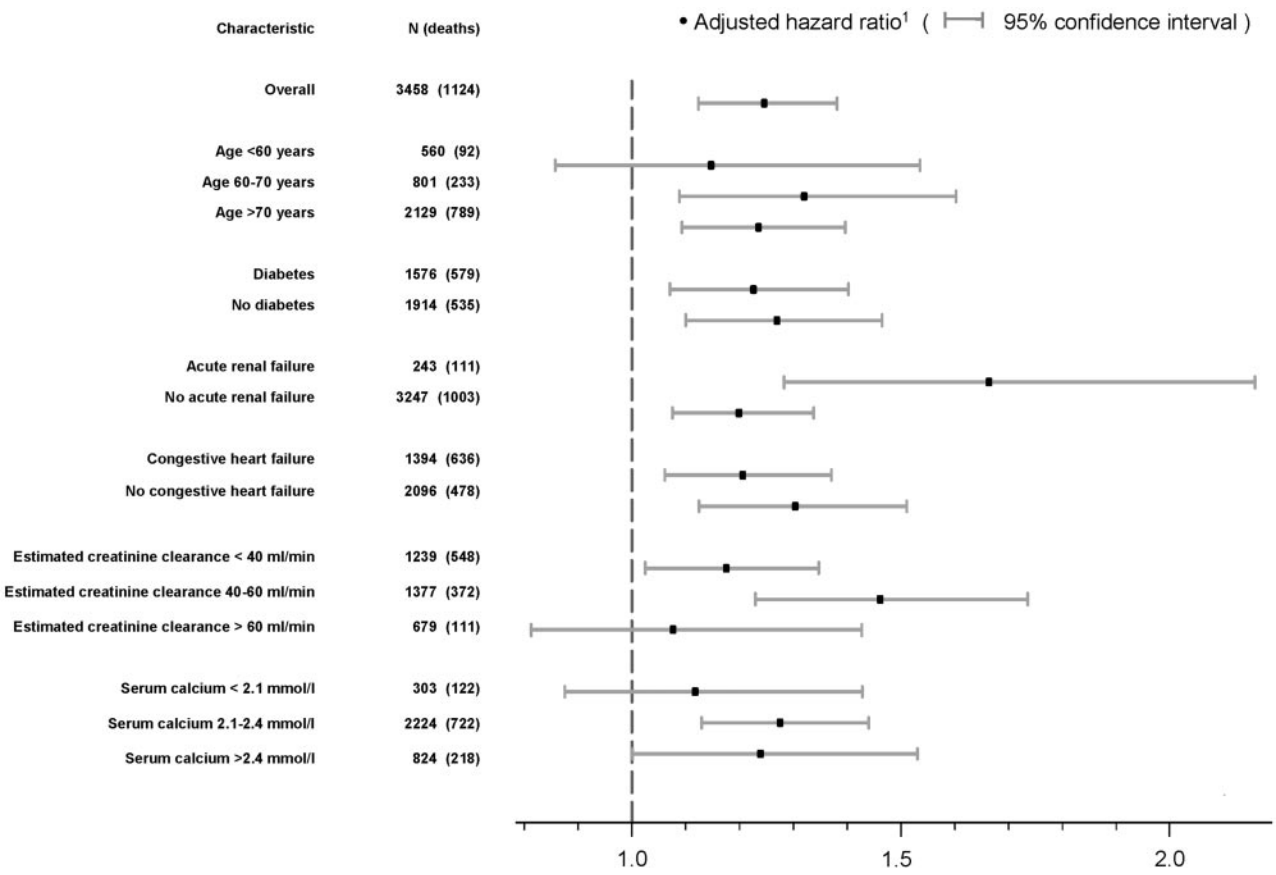

Figure 3. Adjusted hazard of mortality associated with each 1-mg/dl (0.323 mmol/L) increase in serum phosphate level, by subgroup. Model adjusted for age, race, gender, prevalent diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, acute renal failure, calcium intake from medications, hemoglobin, serum calcium, the inverse of baseline creatinine, time-averaged creatinine (area under the curve), slope of creatinine, and maximal creatinine concentration during the baseline period (model 2).

mated CrCl <60 ml/min (9), confirming earlier studies among different CKD populations (7,8).

Our data show considerable variation in serum phosphate levels among CKD patients with similar degrees of functional renal impairment. It is possible that individual variation in phosphate intake and in single-nephron phosphate excretion explain the wide variation in phosphate levels that was observed. Renal phosphate excretion is principally regulated by the type IIa sodium phosphate co-transporter (NP2) located in the proximal tubule (26). Differences in the activity of this transporter or in the levels of phosphaturic factors that modulate this channel (27,28) might lead to different steady-state phosphate concentrations.

Potential limitations of the present study include the restriction of the analyses to patients with a phosphate measurement; the ethnically homogeneous, predominantly male study population; and confounding by additional factors not measured in our study. Although patients who had phosphate measurements tended to have a greater burden of comorbid conditions as compared with those without a phosphate measurement, the association between elevated serum phosphate levels and mortality remained robust across patients with and without these conditions. Our study population of predominantly older, white men raises the question of whether phosphate might have differing effects among other CKD populations. These results should be confirmed in populations that contain a higher proportion of younger, female patients and other ethnic groups. Because serum phosphate levels were ascertained over a relatively long period (up to 18 mo before the study start date), it is possible that these baseline values were not reflective of phosphate levels at the study start. However, the potential misclassification of serum phosphate levels is likely to be nondifferential, resulting in a lower observed relative risk between phosphate and mortality.

The association between serum phosphate levels and mortality may be due to other factors associated with increased serum phosphate. Although phosphate remained significantly and independently associated with mortality after simultaneous adjustment for the creatinine level at study start, time-averaged creatinine (area under the curve) during the baseline period, slope of creatinine change, the maximal creatinine level, and a history of acute renal failure, it is still possible that renal function is confounding our analyses, as a result of the imprecise relationship between serum creatinine levels and renal function. Higher phosphate levels were also associated with a greater prevalence of cardiovascular disease and cardiovascu-

lar medication use, suggesting that phosphate is a marker of comorbidity. The association between phosphate levels and baseline cardiovascular illness adds further suggestive evidence linking phosphate to cardiovascular disease. It is possible that increased phosphate intake is associated with the intake of other nutrients, such as protein and saturated fats, which might increase the subsequent risk for mortality and MI. We found higher phosphate levels to be modestly, although not significantly, correlated with triglyceride levels; however, we found no relationship between phosphate levels and LDL or HDL cholesterol or with body mass index.

Our results do not clarify whether elevated serum phosphate levels are a passive marker for adverse events or actually participate in them. If the latter is true, then modifying phosphate levels might lower the resultant mortality risk. Although strategies to control hyperphosphatemia can be highly effective among the dialysis population, it is unclear whether dietary or pharmacologic intervention could modify the more subtle alterations of serum phosphate observed to be associated with mortality risk in this CKD population.

In summary, we observed an independent association between elevated serum phosphate levels and the risk for mortality and MI among a cohort of veterans with CKD. Further work is needed to confirm these results in other CKD populations and to clarify the mechanism relating phosphate excess to adverse outcomes among people with renal disease.

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