CLINICAL RESEARCH STUDY

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Phosphorus and Risk of Renal Failure in Subjects with Normal Renal Function

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ABSTRACT

PURPOSE: Whether higher serum phosphorus levels increase risk for kidney disease onset and progression to end-stage renal disease in those with normal renal function is largely unknown. We sought to determine whether higher serum phosphorus levels increase risk for end-stage renal disease within a large ethnically diverse population with normal kidney function.

METHODS: A retrospective longitudinal cohort study was performed in the period January 1, 1998 through December 31, 2008 of adults within a vertically integrated health plan (3.4 million members). The primary objective was to determine risk of incident end-stage renal disease. Baseline and time-averaged phosphorus were used for Cox regressions analyses to calculate hazard ratios (HR) adjusting for age, sex, race, pre-existing hypertension, and diabetes.

RESULTS: A total of 94,989 subjects were identified in the 11-year observation period. Mean age of the cohort was 50 years, with 61% female, 38% white, 14% black, and 25% Hispanic. Population-based phosphorus quartile ranges were 1.9-3.0 mg/dL, 3.1-3.4 mg/dL, 3.5-3.8 mg/dL, and 3.9-5.7 mg/dL. End-stage renal disease occurred in 130 (0.1%) subjects. Every 0.5-mg/dL phosphorus increase demonstrated an adjusted HR of 1.40 (95% confidence interval [CI], 1.06-1.84) and HR for mortality of 1.09 (95% CI, 1.06-1.13). Adjusted HRs were 0.64 (95% CI, 0.37-1.11), 0.83 (95% CI, 0.50-1.39), and 1.48 (95% CI, 0.96-2.28) in the 2nd, 3rd, and 4th quartile, respectively, compared with the first phosphorus quartile. Time-averaged serum phosphorus demonstrated a similar relationship across quartiles and as a continuous variable.

CONCLUSION: In our large, ethnically diverse cohort of non kidney disease subjects, higher serum phosphorus levels were associated with greater risk for end-stage renal disease and mortality.

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KEYWORDS: End-stage renal disease risk; Epidemiology; Outcomes; Phosphorus

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Abnormalities in serum phosphorus levels within the end-stage renal disease population have been associated with worsened outcomes, including mortality. This is particularly evident in those with phosphorus in the higher end of the spectrum.[1-3] The putative mechanism of higher phosphorus burden and worsened outcomes speaks largely to vascular pathology.[4-8] The effect of serum phosphorus on kidney disease itself remains uncertain. In nondialysis chronic kidney disease and nonchronic kidney disease populations, small increases in phosphorus levels, even within normal ranges, have been shown to be associated with greater mortality and cardiovascular outcomes.[9-11] In subjects with advanced chronic kidney disease, higher serum phosphorus

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levels have been shown to predict increased incidence of end-stage renal disease, suggesting that phosphorus elevations may adversely affect kidney function.[12-15] To our knowledge, phosphorus levels and end-stage renal disease outcomes have not been studied in those with intact kidney function and free of chronic kidney disease.

Previous observations of phosphorus outcomes in chronic kidney disease populations have had limitations due to smaller sizes and samplings of homogeneous populations using single baseline phosphorus values. In particular, a majority of those studies that have evaluated the relationship between phosphorus and progression of kidney disease have used single baseline serum phosphorus measurements to evaluate outcomes. Thus, the cumulative impact of changing serum phosphorus levels on progression of kidney disease is not accounted for.[13-15] In the current study, we examined whether differences in both baseline and time-averaged serum phosphorus levels (where available) affected end-stage renal disease outcomes within a large, ethnically diverse population of subjects who were free of chronic kidney disease.

CLINICAL SIGNIFICANCE

- There is a high burden of chronic kidney disease (20 million) and end-stage renal disease (300,000) in the US.
- Early detection of markers such as serum phosphorus can potentially help identify, follow, and modify risk in those with greater predilection for chronic kidney disease and progression to end-stage renal disease.
- Higher serum phosphorus levels may represent a mechanism, intermediary step, or a surrogate marker for chronic kidney disease onset and advancement.

METHODS

Study Population

A retrospective, longitudinal cohort study of Kaiser Permanente Southern California (KPSC) members was performed in the period January 1, 1998 thru December 31, 2008. The KPSC health care system is a prepaid integrated health plan providing comprehensive care to 3.4 million members throughout Southern California, from Bakersfield to San Diego, at 12 medical centers and over 100 satellite clinics. As of December 2008, there were over 2.4 million adult members within KPSC. The population is ethnically and socioeconomically diverse, reflecting both the general population of the practicing area and the overall population in the state of California. All KPSC members have similar coverage benefits and access to health care services, clinic visits, procedures, and co-pays for medications.

The study population included subjects age 18 years and older with a minimum of one serum phosphorus measurement and serum creatinine measurement to establish kidney function using estimated glomerular filtration rate (eGFR). This was calculated from the first available serum creatinine level during the study period using the abbreviated 4-point equation developed for the Modification of Diet in Renal Disease Study.[16] Subjects had to have an eGFR $\geq$60 mL/min/1.73 m^2 at the time of serum phosphorus measurement to be included in the study. All subjects also were required to have 1-year continuous membership in the health care plan before the serum phosphorus measurement in order to accurately capture any comorbidities.

To eliminate any competing risks of death or other adverse clinical outcomes that may be an intermediary cause for elevated phosphorus and progression to end-stage renal disease, subjects were excluded if they had prevalent coronary artery disease, congestive heart failure, and cerebrovascular disease, which were determined by inpatient and outpatient International Classification of Diseases (ICD) diagnoses coding. Subjects who had previous procedural coding for coronary artery bypass grafting, percutaneous coronary intervention, and renal replacement therapy (temporary dialysis or renal transplantation) also were excluded from the study population.

Data Collection and Laboratory Measurements

All health care encounters within KPSC are tracked using a common electronic medical records system. Data, including patient demographics, were extracted from internal computerized records, which included laboratory databases, disease registries, and electronic medical charts. Comorbidities were assessed based on inpatient and outpatient ICD diagnoses coding. All laboratory and coding data were collected from encounters as part of routine clinical care.

Serum phosphorus levels were measured using a standard colorimetric method with normal reference values of 2.7-4.5 mg/dL (Roche Diagnostics, Alameda, Calif). Phosphorus levels were recorded longitudinally where multiple values were available. All initial phosphorus measurements were outpatient serum phosphorus levels, and subsequent phosphorus measurements in those with multiple measurements available included both inpatient and outpatient serum phosphorus levels.

Outcomes and Statistical Analyses

The primary outcome evaluated was incident end-stage renal disease defined as a need for renal replacement therapy with dialysis or transplant or reaching an eGFR of $<$15 mL/min/1.73 m^2. The index time for survival analysis was date of first serum phosphorus measurement. Because mortality is a competing risk for end-stage renal disease,[17] rate and risk of mortality also was assessed based on serum phosphorus. Subjects were followed until reaching the end point of end-stage renal disease, death, disenrollment from the health plan, or until the end of observation (December

31, 2008). Renal replacement therapy, defined as initiation of maintenance hemodialysis, peritoneal dialysis, or renal transplant, was identified from electronic medical records, procedure coding data, and Medicare Form 2728. The causes of end-stage renal disease were identified where available using the Southern California Permanente Medical Group internal database, which is inclusive of all dialysis and renal transplant patients within Kaiser Permanente Southern California.

Both baseline and time-averaged phosphorus levels were evaluated. Time-averaged phosphorus was calculated by weighing each measurement by the time span contributed until subsequent measurement. All subjects were categorized into population-based quartiles by serum phosphorus level, with the lowest quartile serving as the reference category. Descriptive analyses were performed and comparisons of variables between categories of serum phosphorus were completed using analysis of variance and χ^2 tests where applicable.

Unadjusted and multivariable Cox proportional hazard modeling were used to analyze the relationship between serum phosphorus levels and incident end-stage renal disease for both serum phosphorus quartiles and as a continuous variable. To evaluate further the total burden of phosphorus over time on renal function decline, a second model that included time-averaged phosphorus levels was performed as a sensitivity analysis. Multivariable hazard ratios (HR) were calculated with adjustment for potential confounders including age, sex, race, and pre-existing hypertension and diabetes mellitus. These same adjustments were made for time-averaged phosphorus and for analysis using phosphorus as a continuous variable. Linear regressions also were performed if linearity was observed.

All analyses were performed with SAS statistical software (version 9.1; SAS Inc., Cary, NC). The study protocol was approved by the Kaiser Permanente Southern California Institutional Review Board with waiver of the need for informed consent.

RESULTS

Characteristics

A total of 94,989 subjects were identified for inclusion in the study. The majority of the cohort (66%) had a single serum phosphorus measurement, while 15% had 2 phosphorus measurements and 19% had 3 or more phosphorus measurements available for analysis. The mean duration of membership for the entire cohort was 8.0 years, with an SD of 3.1 years. The median follow-up duration within the observation window was 4.3 years, with 28,885 subjects having over 3 years of follow-up. A total of 14,841 subjects were excluded due to pre-existing cardiovascular and cerebrovascular disease identified within 1 year before the serum phosphorus measurement. Baseline characteristics of the cohort revealed a mean age of 50 years, with 60.7% female, 37.6% white, and 13.6% black. Hypertension was existent in 38.2% and diabetes mellitus in 14.0% (**Table 1**).

Table 1 Characteristics of Study Cohort

Characteristics	n = 94,989
Age, years ± SD (n)	50.5 ± 15.6 (94,989)
18-49, % (n)	48.4 (45,942)
50-59, % (n)	24.1 (22,906)
60-69, % (n)	15.9 (15,112)
≥70, % (n)	11.6 (11,029)
Sex	
Female, % (n)	60.7 (57,630)
Male, % (n)	39.3 (37,359)
Race	
White, % (n)	37.6 (35,721)
Black, % (n)	13.6 (12,905)
Hispanic, % (n)	25.3 (23,994)
Asian/Pacific, % (n)	6.6 (6250)
Other, % (n)	17 (16,119)
eGFR, mL/min/1.73 m^2	
60-89, % (n)	46.5 (44,179)
≥90, % (n)	53.5 (50,810)
Charlson Comorbidity Index	
0, % (n)	65.7 (62,449)
1, % (n)	15.6 (14,808)
2-4, % (n)	13.1 (12,444)
≥5, % (n)	5.6 (5288)
Pre-existing HTN, % (n)	38.2 (36,295)
Pre-existing DM, % (n)	14 (13,255)

DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension.

There were a total of 10,445 deaths in the cohort within the 11-year observation period.

Subjects were categorized into the following population-based quartiles by baseline serum phosphorus levels: 1.9-3.0 mg/dL (Q1), 3.1-3.4 mg/dL (Q2), 3.5-3.8 mg/dL (Q3), and 3.9-5.7 (Q4). Baseline characteristics of participants stratified by quartile of serum phosphorus are shown in **Table 2**. Age was similar across all quartiles. Females had greater representation with higher quartiles (53.0% in Q1 to 66.9% in Q4). The highest phosphorus quartile had the lowest percentage of Blacks (10.9% vs. 16.3% in Q1), whereas the proportion of Hispanics tended to be slightly greater with higher phosphorus quartiles (24.6% to 26.5%). Diabetes was more prevalent with higher phosphorus quartiles (13.1, 13.8, 13.8, and 14.9%), while hypertension rates were relatively similar across different phosphorus quartiles. Distribution of crude mortality rates (%) were 12.2, 10.8, 10.1, and 10.8 for phosphorus quartiles 1, 2, 3, and 4, respectively. Adjusted HR demonstrated mortality HR of 1.09 (95% confidence interval [CI], 10.6-1.13) for every 0.5-mg/dL serum phosphorus increase.

End-stage Renal Disease Outcomes

A total of 130 (0.1%) reached the primary outcome of end-stage renal disease. The cause of end-stage renal disease was identified in 121 subjects. Diabetes was the most common cause of end-stage renal disease, accounting for

Table 2 Characteristics of Individuals Stratified by Quartiles of Serum Phosphorus Level

	Baseline Serum Phosphorus (mg/dL)				
	1.9-3.0 (n = 23,288)	3.1-3.4 (n = 22,404)	3.5-3.8 (n = 23,218)	3.9-5.7 (n = 26,079)	*P* Value
Age, years ± SD	50.8 ± 15.6	51.1 ± 15.5	50.8 ± 15.6	49.6 ± 15.7	<.001
Sex					<.001
Female, % (n)	53.0 (12,338)	58.5 (13,105)	63.5 (14,750)	66.9 (17,437)	
Male, % (n)	47.0 (10,950)	41.5 (9299)	36.5 (8468)	33.1 (8642)	
Race					<.001
White, % (n)	36.8 (8574)	37.8 (8466)	37.1 (8607)	38.6 (10,074)	
Black, % (n)	16.3 (3796)	14.6 (3276)	12.9 (2997)	10.9 (2836)	
Hispanic, % (n)	24.6 (5719)	24.5 (5482)	25.3 (5874)	26.5 (6919)	
Asian/Pacific, % (n)	6.1 (1418)	6.0 (1355)	6.9 (1603)	7.2 (1874)	
Other, % (n)	16.2 (3781)	17.1 (3825)	17.8 (4137)	16.8 (4376)	
eGFR, mg/mL/1.73 m^2					<.001
60-89, % (n)	47.3 (11,021)	47.0 (10,527)	46.5 (10,798)	45.4 (11,833)	
≥90, % (n)	52.7 (12,267)	53.0 (11,877)	53.5 (12,420)	54.6 (14,246)	
Charlson Comorbidity Index, % (n)					<.001
0, % (n)	67.2 (15,660)	66.8 (14,962)	66.3 (15,399)	63.0 (16,428)	
1, % (n)	15.4 (3577)	15.7 (3510)	15.4 (3585)	15.9 (4136)	
2-4, % (n)	12.1 (2817)	12.4 (2771)	13.1 (3040)	14.6 (3816)	
≥5, % (n)	5.3 (1234)	5.2 (1161)	5.1 (1194)	6.5 (1699)	
Pre-existing HTN, % (n)	38.4 (8942)	39.0 (8739)	38.0 (8816)	37.6 (9798)	<.001
Pre-existing DM, % (n)	13.1 (3060)	13.8 (3085)	13.8 (3212)	14.9 (3898)	<.001

DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension.

32%. Eighteen (15%) cases of end-stage renal disease were attributed to acute kidney injury, and these cases were distributed evenly across ranges of phosphorus. The mean duration between the first eGFR and end-stage renal disease was 2.8 years, with an SD of 1.9. The majority (79 subjects) had follow-up of >3 years and the average duration for progression to end-stage renal disease in those subjects was 3.7 years, with an SD of 2.0.

Unadjusted and adjusted HR for end-stage renal disease demonstrated a trend for greater risk with rising serum phosphorus levels (**Figure 1**, **Table 3** **and** **Table 4**). Every 0.5-mg/dL phosphorus elevation was associated with HR for end-stage renal disease of 1.40 (95% CI, 1.06-1.84). This relationship was attenuated in the subanalysis of the population who had >3 years' follow-up, which revealed an HR of 1.04 (95% CI, 0.91-1.19) for every 0.5-mg/dL phosphorus increase.

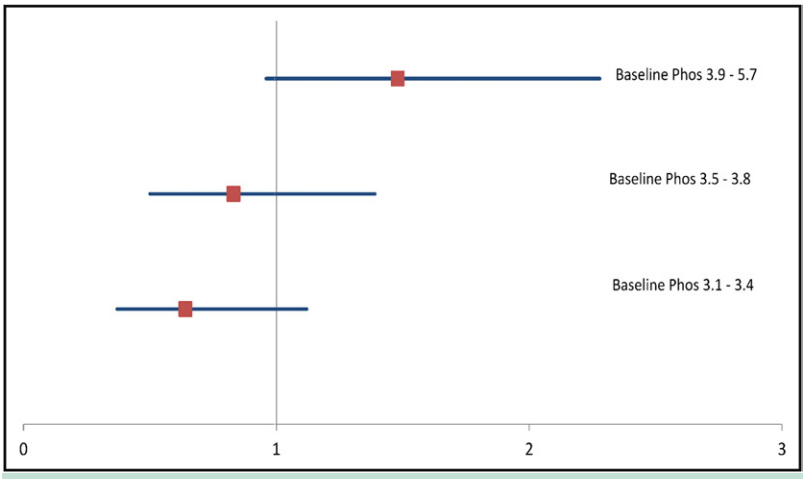

Figure 1 Multivariate adjusted hazard ratio (95% confidence interval) for end-stage renal disease associated with various quartiles of serum phosphorus compared with reference range of 1.9-3.1 mg/dL.

Table 3 Multivariable Cox Regression Analysis (95% CI) for ESRD by Baseline Serum Phosphorus Level (Adjusted for Age, Race, Sex, DM, HTN)

Variable	Adjusted HR (95% CI)	*P* Value
Phosphorus quartile		<.001
1.9-3.0	Reference	
3.1-3.4	0.64 (0.37-1.11)	
3.5-3.8	0.83 (0.49-1.39)	
3.9-5.7	1.48 (0.96-2.28)	
Sex		<.001
Male vs female	2.42 (1.70-3.45)	
Race		<.001
Black vs white	2.69 (1.67-4.33)	
Hispanic vs white	2.24 (1.43-3.50)	
Asian vs white	0.96 (0.40-2.29)	
Pre-existing HTN		<.001
Yes vs no	1.79 (1.18-2.72)	
Pre-existing DM		<.001
Yes vs no	6.79 (4.61-10.00)	

CI = confidence interval; DM = diabetes mellitus; ESRD = end-stage renal disease; HTN = hypertension.

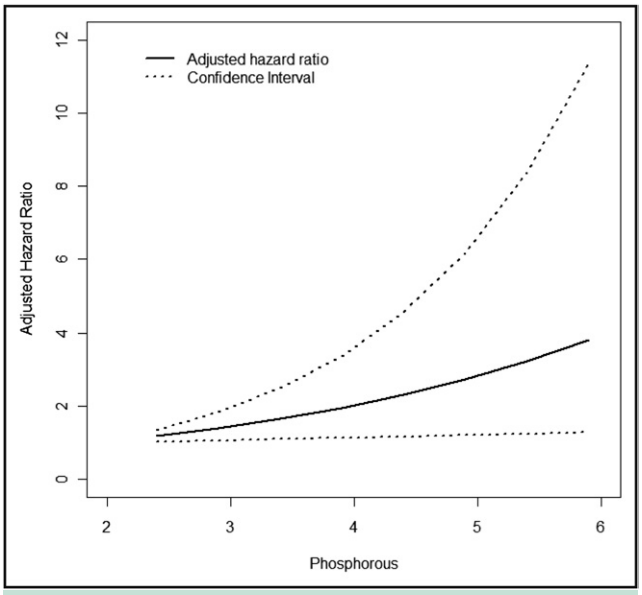

Figure 2 Adjusted hazard ratios with 95% confidence intervals for end-stage renal disease-based serum phosphorus levels. Rising serum phosphorus shows a positive trend/relationship with risk for end-stage renal disease.

The highest serum phosphorus quartile, with a range of 3.9-5.7 mg/dL, was associated with the highest HR for end-stage renal disease in both adjusted and unadjusted models. The adjusted HRs (95% CI) for end-stage renal disease after adjustment for age, race, sex, eGFR, pre-existing diabetes mellitus, and pre-existing hypertension compared with the lowest phosphorus quartile were 0.64 (0.37-1.11), 0.83 (0.50-1.39), and 1.48 (0.96-2.28) in the 2nd, 3rd, and 4th quartiles, respectively. Male sex (HR 2.42; 95% CI, 1.70-3.45), black race (HR 2.69; 95% CI, 1.67-4.33), pre-existing hypertension (HR 1.79; 95% CI, 1.18-2.72), and pre-existing diabetes mellitus (HR 6.79; 95% CI, 4.61-10.00) also were independently associated with increased HRs for end-stage renal disease. **Figure 2** shows the adjusted HR (95% CI) across ranges of serum phosphorus, illustrating the linear risk of end-stage renal disease with rising phosphorus levels starting at about 3.1 mg/dL and higher.

To minimize potential confounding from acute and temporary fluctuations in serum phosphorus, all analyses were repeated using time-averaged serum phosphorus levels. In these analyses, there remained an association between quartile of serum phosphorus and incidence of end-stage renal disease (**Table 5**). Time-averaged serum phosphorus levels demonstrated adjusted HR (95% CI) of 0.81 (0.41-1.59), 1.33 (0.73-2.43), and 4.16 (2.50-6.95) in the 2nd, 3rd, and 4th quartiles, respectively. The HR was 1.82 (95% CI, 1.52-2.17) for every 0.5-mg/dL phosphorus increase when using time-averaged phosphorus as a continuous variable (**Table 4**). These results did not change substantially in sensitivity analyses when the models were adjusted for calcium (results not shown).

Table 4 Multivariate Adjusted Linear Regressions Associated with a 0.5-mg/dL Higher Serum Phosphorus Level

	Hazard Ratios (95% CI) for ESRD
Baseline phosphorus	1.40 (1.06-1.84)
Time-averaged phosphorus	1.82 (1.52-2.17)

CI = confidence interval; ESRD = end-stage renal disease.

Table 5 Multivariable Cox Regression Analysis (95% CI) for ESRD by Time-averaged Serum Phosphorus (Adjusted for Age, Race, Sex, DM, HTN)

Variable	Adjusted HR (95% CI)	*P* Value
Phosphorus quartile		<.001
1.9-3.0	Reference	
3.1-3.4	0.81 (0.41-1.59)	
3.5-3.8	1.33 (0.73-2.43)	
3.9-5.7	4.16 (2.50-6.95)	
Sex		<.001
Male vs Female	2.76 (1.94-3.93)	
Race		<.001
Black vs white	2.85 (1.77-4.58)	
Hispanic vs white	2.26 (1.45-3.54)	
Asian vs white	0.96 (0.40-2.29)	
Pre-existing HTN		<.001
Yes vs no	1.81 (1.19-2.75)	
Pre-existing DM		<.001
Yes vs no	6.45 (4.37-9.51)	

CI = confidence interval; DM = diabetes mellitus; ESRD = end-stage renal disease; HR = hazard ratio; HTN = hypertension.

DISCUSSION

Main Findings

In our large, ethnically diverse population of nonchronic kidney disease subjects, we found a graded, independent association between higher serum phosphorus levels and risk of end-stage renal disease. This association remained even after adjustment for age, race, sex, eGFR, hypertension, and diabetes. Serum phosphorus levels above 3.1 mg/dL were associated with increased end-stage renal disease risk. This relationship was present despite the fact that phosphorus levels for the most part were within normal reference ranges. These findings were demonstrated using baseline serum phosphorus, but the association was stronger when evaluating time-averaged serum phosphorus levels. In subjects with normal kidney function (eGFR $\geq$60 mL/min/1.73 m^2), every 0.5-mg/dL phosphorus increase demonstrated a 40% greater risk for incident end-stage renal disease.

Traditional risk factors including hypertension, diabetes, and black race also were associated with increased risk for end-stage renal disease. In turn, characteristics that were associated with higher serum phosphorus level in and of itself included female sex, diabetes, and Hispanic ethnicity/race.

Implications

Past observations have found that abnormalities in serum phosphorus, both low and high levels, are associated with higher mortality in patients with end-stage renal disease.[1-3] The association between serum phosphorus levels and the risk of progression of chronic kidney disease also has been shown in previous observations on subjects with advanced chronic kidney disease. However, the impact of phosphorus on outcomes in the general population is less well described.[11,13-15,18] One epidemiologic study by Schwarz et al[13] evaluated 985 male Veterans Affairs patients with advanced stages of chronic kidney disease and found that higher baseline serum phosphorus was associated with greater risk of renal function decline. A baseline serum phosphorus >4.3 mg/dL compared with <3.3 was shown to have an HR of 1.6 for end-stage renal disease or doubling of creatinine. Kovesdy and Kalantar-Zadeh[12] found not only an association between baseline serum phosphorus levels and progression of kidney disease, but also a stronger association when examining time-averaged serum phosphorus levels. Our results support these previous findings and also emphasize the importance of the cumulative burden of hyperphosphatemia on kidney disease/damage. Admittedly, time-averaged phosphorus could have been due to progressive decline in renal function and may be reflective of kidney disease rather than a cause of renal damage. Another confounder on progression to end-stage renal disease is the competing risk of death on the chronic kidney disease population.[17] While the crude rates of mortality showed higher rates in lower and higher phosphorus quartiles, the adjusted HR showed a higher risk for mortality with increasing phosphorus levels, paralleling the relationship between phosphorus and end-stage renal disease. Thus, the 40% increase in risk for end-stage renal disease may be underestimated because higher phosphorus subjects also were more likely to die and never reach end-stage renal disease.

Our study demonstrated a positive relationship between rising serum phosphorus and risk of end-stage renal disease, which may not have been as apparent when assessing this relationship using artificial phosphorus quartiles as we did in our analysis. When the ranges of serum phosphorus are combined into 4 groups, the comparisons may not be as demonstrative or fail to detect the differences that are found in a comparison using phosphorus as a continuous variable, where broader ranges with more discrete values are used for comparisons. Thus, the HR based on the continuous phosphorus variable is more sensitive in detecting this relationship and association.

To our knowledge, the present study is the first to examine the relationship of baseline and time-averaged serum phosphorus on the risk of end-stage renal disease in subjects with normal kidney function.[1-3] Nonchronic kidney disease subjects were identified as those with documented eGFR $\geq$60 mL/min/1.73 m^2. This operational definition represents a broad range of renal function, as there is a greater tendency for imprecision of the Modification of Diet in Renal Disease equation in this higher range of eGFR.[19,20] Thus, within this population, the disparities in serum phosphorus and outcomes may be a reflection of renal function rather than the serum phosphorus level. However, this is very unlikely, as phosphorus elevations do not occur in chronic kidney disease until creatinine clearance reaches <50 mL/min.[21] The time-averaged serum phosphorus analysis similarly revealed that the highest phosphorus quartile (3.9-5.7 mg/dL) was associated with the highest adjusted HR (4.16; 95% CI, 2.50-6.95) for end-stage renal disease when compared with the lowest quartile. The time-averaged serum phosphorus as a continuous variable showed a more robust relationship where a 0.5-mg/dL increase had an adjusted HR (95% CI) for end-stage renal disease of 1.82 (1.52-2.17).

A potential mechanism underlying serum phosphorus levels and kidney disease onset or progression may be due to increased nephrocalcinosis,[22-25] where higher levels of serum phosphorus have been postulated to directly promote vascular injury and calcifications.[5,7,8,26] These underlying damages also may increase risk for irreversible acute kidney injury, as was the causative mechanism in 15% of the end-stage renal disease cohort in our study. The elevated serum phosphorus also might reflect those with secondary hyperparathyroidism, which has been associated with adverse outcomes, particularly in individuals with impaired kidney function.[22-25] However, secondary hyperparathyroidism would have been unlikely in this cohort given the relatively preserved renal function in the study population.

Serum fibroblast growth factor-23 (FGF-23) has been shown to be a key regulator of serum phosphorus levels in chronic kidney disease patients.[15,27,28] FGF-23 concentrations have been found to increase early in the course of

chronic kidney disease, before the development of overt hyperphosphatemia.[4,27,29] Stimulation of the FGF receptor increases the production of angiotensin-converting enzyme and may activate the renin-angiotensin system, possibly facilitating the progression of kidney damage.[27,28,30] A study of 1099 individuals by Kendrick et al[31] found higher incidence of dialysis initiation across increasing FGF-23 quartiles in subjects with mild chronic kidney disease and with serum phosphorus levels in over 50% of subjects within normal range.[31] In end-stage renal disease, FGF-23 has been demonstrated to increase risk of mortality.[32] Furthermore, in animal models, FGF-23 has been shown to cause reversible cardiac left ventricular hypertrophy.[33] Overall, however, the role of FGF-23 with phosphorus and progression of kidney disease remains experimental and largely unknown.

Strengths and Limitations

The present study has several limitations. This study included a large, ethnically diverse group of subjects with an extensive follow-up period of up to 11 years who had serum phosphorus levels drawn as part of routine clinical care. However, parathyroid hormone levels and 1, 25-dihydroxyvitamin D levels were not available for further evaluation on a majority of subjects. Calcium levels were available on a majority of subjects and a separate analysis evaluating the association between serum calcium levels and risk of end-stage renal disease did not show statistical significance. In addition, simultaneous adjustment and evaluation of serum calcium levels were not found to be a significant confounder in relation to serum phosphorus levels and progression of kidney disease (data not shown). Due to lack of availability, neither FGF-23 nor Klotho protein concentration levels were available for evaluation and further insight into mechanisms underlying the association between phosphorus levels and end-stage renal disease risk. Information on the use of phosphorus binders, angiotensin-converting enzyme inhibitors, vitamin D analogues, or other nutritional supplements and diet were not available. It is notable that use of phosphorus binders across different phosphorus levels in chronic kidney disease have been associated with improved mortality outcomes.[34] Estimated GFR was used as a measure of kidney function rather than a more precise measurement of kidney function, and imprecision related to this method also may have affected results. More importantly, we could not definitively exclude renal function as an intermediary or causative mechanism for the elevation in serum phosphorus, although we included only those with eGFR $\geq$60 mL/min/1.73 m^2 documented at the same time as the first or baseline serum phosphorus measurement, but did not follow additional eGFRs in those who had subsequent measurements. This may be more evident in the time-averaged serum phosphorus analyses, where the changing and rising phosphorus may just as equally be due to worsening renal function versus phosphorus-related damage to the kidney. In our relatively normal kidney function population, we found a 40% greater risk of progressing to end-stage renal disease with every 0.5-mg/dL phosphorus increase. Finally, given the retrospective, observational nature of this study, a causal relationship between serum phosphorus concentrations and end-stage renal disease risk cannot be established. In addition, caution is advised in advocating lowering of phosphorus to extreme levels, as hypophosphatemia itself lends risks to various clinical complications, including myopathy, bone disorders, respiratory distress, and encephalopathy.[35-38] Hypophosphatemia in the chronic kidney disease populations have been associated with poor nutritional status and worsened mortality outcomes.[3,39]

CONCLUSIONS

Higher levels of serum phosphorus were associated with increased risk of end-stage renal disease in our large, ethnically diverse population of subjects who had kidney function within normal ranges. Further studies are needed to determine a mechanism for this association between phosphorus and progression/onset of kidney disease and whether there is utility of strategies to maintain lower phosphorus on preservation of renal function.

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