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Article

Chronic Kidney Disease Progression and Outcome According to Serum Phosphorus in Mild-to-Moderate Kidney Dysfunction

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Summary

Background and objectives Several factors might alter serum phosphate homeostasis and induce hyperhosphatemia in patients with chronic kidney disease (CKD) not requiring dialysis. However, whether and to what extent hyperphosphatemia is associated with a poor prognosis in different CKD patient groups remain to be elucidated.

Design, setting, participants & measurements We utilized the "Prevenzione Insufficienza Renale Progressiva" (PIRP) database, a large project sponsored by the Emilia-Romagna Health Institute. PIRP is a collaborative network of nephrologists and general practitioners located in the Emilia-Romagna region, Italy, aimed at increasing awareness of CKD complications and optimizing CKD patient care. We identified 1716 patients who underwent a GFR and serum phosphorous assessment between 2004 and 2007. We tested whether phosphate levels ≥4.3 mg/dl are associated with the risk of CKD progression or all causes of death.

Results Older age and male sex were associated with lower phosphate levels. Instead, higher phosphate levels were noted in patients with diabetes. Patients with phosphate levels ≥4.3 mg/dl were at an increased risk of starting dialysis or dying (hazard ratio 2.04; 95% confidence interval [1.44, 2.90]). Notably, subgroup analyses revealed that the magnitude of the risk associated with hyperphosphatemia varied depending on age, sex, diabetes, and different stages of CKD.

Conclusions These analyses lend support to the hypothesis that phosphorous abnormalities might have a negative effect on the residual renal function and prognosis in different groups of CKD patients. However, the risk associated with hyperphosphatemia might vary in specific CKD patient subgroups.

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Introduction

Over the past 10 years a growing body of evidence has been built up suggesting a link between serum levels of bone minerals, vitamin D, intact parathyroid hormones (iPTH), the cardiovascular system, and mortality. These associations were first detected in large data sets of patients on dialysis (1–3) and only recently have similar links been confirmed in chronic kidney disease (CKD) not requiring dialysis (4) and in people with normal kidney function (5–8).

Nonetheless, despite a large and convincing body of evidence suggesting a robust association between serum phosphorous levels and all-cause mortality in dialysis-dependent individuals, (2,3) only a few papers have investigated the adverse effects of hyperphosphatemia on kidney function and prognosis in CKD individuals (9–14). Notably, these papers did not test whether the toxicity associated with hyperphosphatemia is quantitatively or qualitatively different in men and women, persons with diabetes, the elderly, and different stages of CKD. Indeed, serum phosphorus is under the control of three dynamically interacting factors: diet intake, the net amount removed by the bone, and the quota excreted by the kidneys. Several experimental and observational studies suggest that the relative contribution of these factors to hyperphosphatemia may vary in different subgroups of individuals. Thus, the higher levels of serum phosphorus reported in women, persons with diabetes, and young individuals may reflect different pathologic conditions and may be associated with a different prognostic significance. In this regard, two previous papers by Onufrak and co-workers (6,15) suggest that the adverse effect of serum phosphorus on the cardiovascular system and mortality might be limited to men from the general population (6,15).

We sought to investigate the robustness of the as-

sociation between hyperphosphatemia and progression to ESRD as well as all-cause mortality in the overall study cohort and in different subgroups of CKD patients not receiving dialysis.

Materials and Methods

Patients

We used the patient records from the "Prevenzione Insufficienza Renale Progressiva" (PIRP) database, a large project sponsored by the Emilia-Romagna Health Institute. The PIRP project is a collaborative network of nephrologists and general practitioners located in the region of Emilia-Romagna, Italy, aimed at increasing awareness of CKD complications and optimizing CKD patient care. Demographic, clinical, and laboratory characteristics of all consecutive patients referred to a nephrology center are added to the PIRP database. From the original database, we identified all of the patients who underwent a GFR (estimated GFR) and serum phosphorous assessment from the date the PIRP project began (July 2004) to the last available update of the list of deaths of the "Agenzia Sanitaria e Sociale Regionale- Regione Emilia-Romagna." This agency provided the PIRP investigators with the official list of patients registered in the PIRP data set who died during the follow-up (from July 2004 to December 2007).

The diabetes classification was based on having either an 8-hour fasting plasma glucose level ≥126 mg/dl, a nonfasting plasma glucose >200 mg/dl, or whether the patient reported having diabetes or was taking diabetes medications. Hypertension was defined as a diastolic BP ≥90 mmHg, systolic pressure ≥140 mmHg, or self-report of taking medication for hypertension. Chronic obstructive pulmonary disease (COPD) was defined if the patient reported having COPD. Cardiovascular disease (CVD) was defined as a history of cardiac arrhythmia, peripheral vascular disease, cerebral vasculopathy, ischemic heart disease, or chronic heart failure.

Laboratory Methods

Measurement of serum phosphorus, creatinine, and other biomarkers was performed at the time of PIRP project inception in a fasting state at each study site. All of the laboratories used a serum creatinine analysis calibrated against an isotope dilution mass spectrometry (IDMS) reference standard. The estimated GFR (eGFR) was determined through the Modification of Diet in Renal Disease (MDRD) equation for standardized serum creatinine values (16).

Due to the fact that the PIRP is a collaborative project with the general practitioners in the Emilia-Romagna region rather than an observational study, parathyroid hormone and 25OH vitamin D levels were not standardized and were not included in the analysis.

Study Outcomes

For this study we examined the association between phosphorus and three outcomes: (*1*) the composite event of progression to ESRD or death, whichever came first; (*2*) progression to ESRD defined as the need for renal replacement therapy; (*3*) all-cause mortality. Indeed, these are the most clinically relevant outcomes for CKD patients. Nonetheless, considering the association between fast renal function deterioration and risk of death, (17) it is important to test the effect of phosphorus on the combination of the two outcomes before testing the effect of phosphorus on each of the two outcomes separately. Furthermore, the association between phosphorus and outcome was tested in different CKD patient subgroups. Clinical outcome adjudication is systematically performed at 6 monthly intervals. The date of dialysis inception is identified through the Italian Registry of Dialysis or, alternatively, by the renal unit where the patient started RRT. Deaths among cohort members are identified through the review of the official list of deaths provided by the Italian local government agency "Agenzia Sanitaria e Sociale Regionale- Regione Emilia-Romagna", as well as by means of a regular follow-up by the physician at each study site.

Statistical Analyses

As serum phosphorus does not seem to be linearly associated with the clinical outcome (Figure 1B) and the risk of clinical outcome increases significantly for serum phosphorus above the 75th percentile of the serum distribution, the patients were grouped into four strands based upon quartile of serum phosphorus at baseline. Continuous demographic, clinical, laboratory variables are presented as mean and SD or median and interquartile range (IQ) when appropriate. Categorical variables are expressed as proportions. Trends across quartiles of phosphorus were compared using ANOVA for continuous variables and χ^2 tests for discrete variables. To gauge the association between serum phosphorus and the primary end point, we first plotted the incidence of the composite end point curves according to phosphorus quartiles using the Kaplan-Meier product-limit method and we used the two-sided log rank test to calculate overall P value for survival differences (18). Next, we calculated the age and multivariable adjusted hazard ratios (HR) by fitting the data to Cox proportional hazard models (19).

The robustness of the association between serum phosphorus and clinical outcome was tested by progressively adding variables to the models that might have an effect on serum phosphorus or the clinical outcome considered. All of the models presented are age-adjusted, case mix–adjusted (adjusted for age, sex, eGFR, history of diabetes mellitus, history of hypertension, and history of COPD and CVD), and lastly, fully adjusted (age + case mix + hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use). We tested all of the variables to ensure they satisfied the proportional hazards assumption. The model's predictive performance was internally validated by means of a nonparametric bootstrapping process (20,21). The effect modification of variables that could modulate the association between hyperphosphatemia and the composite outcome was explored by performing subgroup analyses and by inclusion of interaction terms. In view of the relatively small number of events in each subgroup and the competitive nature of the two end points studied, we did not separately test the association between hyperhosphatemia and the two end points. Case deletion was used to handle the missing values. A P value <0.05

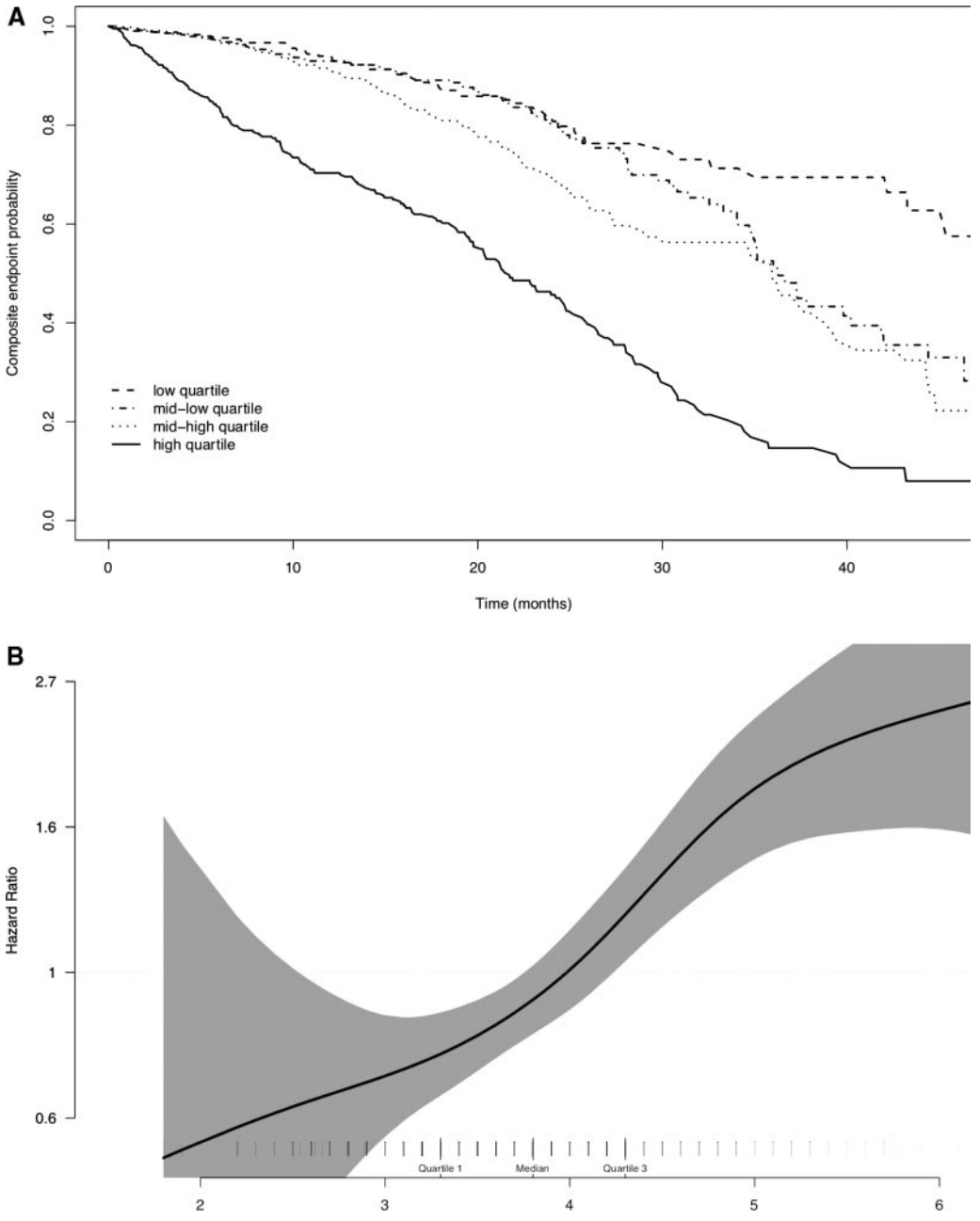

Figure 1. | **(A) Overall likelihood of experiencing the composite end point according to quartile of serum phosphorus.** (B) The HR of experiencing the composite end point according to serum phosphorous levels adjusted for age, case mix, hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use. The solid line represents the HR according to serum phosphorous level; the grey area represents the 95% CI.

was considered statistically significant. All analyses were completed using R version 2.9.2 (August 24, 2009) (The R Foundation for Statistical Computing).

Results

The characteristics of the 1716 participants are summarized in Table 1. Greater levels of phosphorus were noted in women and in young patients as well as in association with diabetes mellitus, severe renal impairment, low levels of serum calcium and hemoglobin, and with the use of vitamin D and calcium salts (Table 1).

During an average follow-up of 1.3 ± 0.94 (median 1.15, IQ 0.59 to 1.91) years, 451 patients died or progressed to ESRD and began dialysis (composite end point rate: 202 of 1000 patients-year, 95% confidence interval [CI]: 184, 221). Specifically, 178 patients died (mortality rate: 97 of 1000 patients-year, 95% [CI]: 84, 113) and 273 started dialysis (dialysis initiation rate: 137 of 1000 patients-year, 95% CI: 121, 154).

The cumulative incidence of the composite end point (death or dialysis inception) in the overall population differed significantly by phosphorus quartiles (log-rank

Table 1. Demographic, clinical, and laboratory characteristics of the entire study cohort and according to quartiles of phosphorus

Variable	Overall (n = 1716)	Quartiles of Serum Phosphorus				P Trend
		P < 3.3 mg/dl (n = 382)	$P \geq$ 3.3 mg/dl and < 3.8 mg/dl (n = 426)	$P \geq$ 3.8 mg/dl and < 4.3 mg/dl (n = 479)	$P \geq$ 4.3 (n = 429)	
Demographic variables						
age (years)	70.0 (13.6)	72.0 (11.3)	71.6 (12.8)	69.6 (13.9)	67.2 (15.2)	<0.001
male gender (%)	66.2	84.3	68.5	61.4	53.1	<0.001
Clinical variables						
hypertension (%)	96.3	96.1	97.1	96	96.2	0.78
diabetes mellitus (%)	29.0	20.2	25.2	34.0	34.8	0.001
COPD (%)	11.6	12.9	12.8	11.1	9.9	0.47
CVD (%)	36.7	39.8	39.4	35.7	32.6	0.10
CKD (%)						
stage 3	37.0	37.1	30.8	23.7	8.3	<0.001
stage 4	46.6	17.0	25.0	32.8	25.2	<0.001
stage 5	16.2	3.6	10.8	23.3	62.4	<0.001
Laboratory variables						
phosphorus (mg/dl)	3.9 (2.13)	2.9 (0.3)	3.5 (1.4)	4.0 (0.16)	5.2 (3.9)	<0.001
calcium (mg/dl)	9.0 (0.93)	9.1 (1.0)	9.0 (0.9)	9.0 (0.9)	8.8 (0.9)	0.006
iPTH (ng/ml)	178 [73 to 178]	98 [68 to 169]	119 [71 to 185]	117 [75 to 203]	173 [96 to 334]	<0.001
hemoglobin (mg/dl)	12.5 (3.3)	13.2 (1.7)	12.6 (1.6)	12.2 (5.7)	11.6 (1.6)	<0.001
total cholesterol (mg/dl)	192 (42)	191 (41)	191 (40)	193 (45)	193 (43)	0.91
HDL cholesterol (mg/dl)	51.9 (15)	49.5 (13)	51.4 (14)	53.1 (16)	53.8 (16)	0.01
triglycerides (mg/dl)	149 (81)	155 (83)	140 (74)	152 (83)	149 (81)	0.09
uric acid (mg/dl)	6.3 [5.2 to 7.4]	6.3 [5.6 to 7.4]	6.2 [5.6 to 7.4]	6.3 [5.1 to 7.3]	6.2 [5.2 to 7.6]	0.55
glucose (mg/dl)	108 (38)	106 (34)	107 (41)	112 (42)	105 (34)	0.08
creatinine (mg/dl)	2.3 [1.8 to 3.1]	1.9 [1.6 to 2.3]	2.0 [1.7 to 2.7]	2.4 [1.8 to 2.9]	3.2 [2.3 to 4.4]	<0.001
GFR (mg/min per 1.73 m^2)	25 [18 to 34]	32 [25 to 40]	28 [21 to 36]	24 [18 to 32]	17 [12 to 24]	<0.001
Concomitant medications						
calcium salts	15.9	6.4	9.4	14.6	32.5	<0.001
vitamin D	16.1	9.8	13.5	16.7	23.9	<0.001
ARB	31.7	32.1	31.3	33.5	29.9	0.71
ACE inhibitors	46.7	47.2	49.0	47.4	43.3	0.39
other hypertensive medications	24.5	19.4	25.0	24.7	28.5	0.03

Data are expressed as mean (standard deviation) or median [IQR] when appropriate. ARB, Angiotensin Receptor Blockers.

Table 2. Association between hyperphosphatemia and the composite outcome (death or progression to ESRD) in the study cohort

Variable	Overall (n = 1716)								
	Age-Adjusted			Case Mix Model[a]			Cox Full Model[b]		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
$P < 3.3$ mg/dl	0.64	0.42 to 0.96	0.03	0.75	0.49 to 1.14	0.18	0.78	0.51 to 1.19	0.25
$P \geq 3.3$ and < 3.8	Ref			Ref			Ref		
$P \geq 3.8$ and < 4.3	1.29	0.91 to 1.81	0.14	0.98	0.69 to 1.39	0.94	0.93	0.66 to 1.33	0.72
$P \geq 4.3$	4.01	2.93 to 5.47	<0.001	2.32	1.64 to 3.27	<0.001	2.04	1.44 to 2.90	<0.001

[a]Case mix: age + gender, eGFR, history of diabetes mellitus, history of hypertension, and history of COPD and CVD.
[b]Full model: age + case mix + hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use.

test: $P < 0.001$, for all tests) (Figure 1A). Indeed, when compared with the mid-low quartile of phosphorus (phosphorous level ≥3.3 mg/dl and <3.8 mg/dl), a serum level of phosphorus <3.3 mg/dl was associated with the lowest risk (age-adjusted HR: 0.64, 95% CI: [0.42, 0.96]; $P = 0.03$) of experiencing the composite end point. In contrast, a serum phosphorous level ≥4.3 mg/dl was associated with a significant increase in the risk in the composite end point (HR: 4.01, 95% CI: 2.93, 5.47; $P < 0.001$) (Table 2).

We then adjusted for the case mix (*i.e.*, sex, eGFR, history of diabetes mellitus, history of hypertension, and history of COPD and CVD) and the risk of the composite end point was attenuated but remained significantly elevated among patients in the highest quartile of phosphorus (HR 2.32; 95% CI: 1.64, 3.27; $P < 0.001$). By contrast, patients in the lowest quartile of phosphorus did not show a significant reduction in the incidence of the composite end point (HR 0.75; 95% CI: 0.49, 1.14; $P = 0.18$) (Table 2). Noteworthy, further adjustment for different modifiable factors associated with either progression to dialysis or mortality (*i.e.*, hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use) did not substantially change the hazard associated with hyperphosphatemia (HR 2.04; 95% CI: 1.44, 2.90; $P < 0.001$) (Table 2).

Despite the fact that the analyses for the interaction terms did not reveal any statistically significant modification, with the exception of diabetes (significant interaction $P = 0.02$), the subgroup analyses revealed that the hyperphosphatemia magnitude of effect might also vary depending on age, sex, and different stages of CKD (Figure 2). Indeed, a serum phosphorous level above the normality range (*i.e.*, ≥4.3 mg/dl) seems to predict a greater risk of the composite end point in earlier stages of CKD in men, the elderly, and patients with diabetes (Figure 2).

We then separately tested the association between serum phosphate and the risk of death or progression to dialysis. As expected, patients with hyperphosphatemia (phosphorus ≥4.3 mg/dl) were more likely than peers to experience each of the two events (Figures 3 and 4). Indeed, after adjustments for confounders, serum levels of phosphorus ≥4.3 mg/dl was associated with a significant 188% (HR 2.88; CI 1.77, 4.67; $P < 0.001$) and 149% (HR 2.49; 95% CI 1.44, 4.32; $P = 0.001$) increase in the risk of either starting dialysis or of death, respectively (Figures 3 and 4, Table 3).

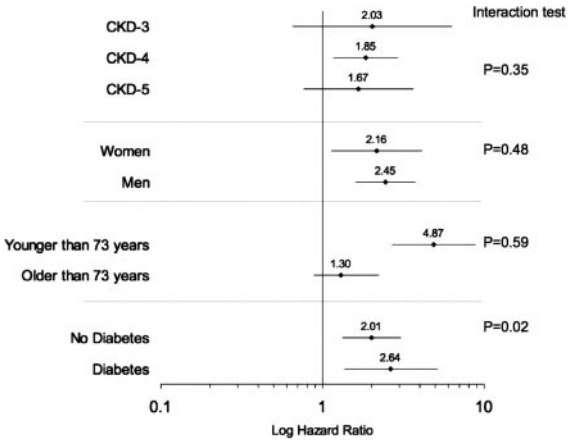

Figure 2. | Association between hyperphosphatemia (serum phosphorus ≥4.3 mg/dl) and the composite outcome (death or progression to ESRD) in different CKD-NDD subgroups. Here are depicted the HR associated with hyperphosphatemia compared with the reference group (serum phosphorus ≥3.3 but <3.8 mg/dl) in different stages of CKD, age category, sex, and diabetes status. All results are adjusted for the case mix and hemoglobin, total calcium, uric acid, ACE inhibitors, vitamin D, and calcium salts use.

Finally, we performed a bootstrap analysis to further examine the strength of the association between phosphorus and the primary end point. The results yielded by this technique confirmed the prognostic validity of the serum phosphorous variable in terms of risk prediction of progression to ESRD or death. Indeed, serum phosphate was selected in almost all of the Cox models calculated with the bootstrap samples. Furthermore, the bootstrap procedure only marginally modified the hazard of the composite end point and the confidence interval associated with hyperphosphatemia (HR 2.04; 95% CI: 1.54, 2.69). Similar findings were also noted for the association between phosphorus and the risk of progression to ESRD (HR 2.86; 95% CI: 1.93, 4.32) or death (HR 1.73; 95% CI: 1.12, 2.77).

Discussion

Our results lend further support to the notion that serum phosphorus is linked to an adverse effect on renal function and prognosis in CKD, independently of other traditional risk factors (22,23). Indeed, progressive adjustment for confounders as well as the bootstrap anal-

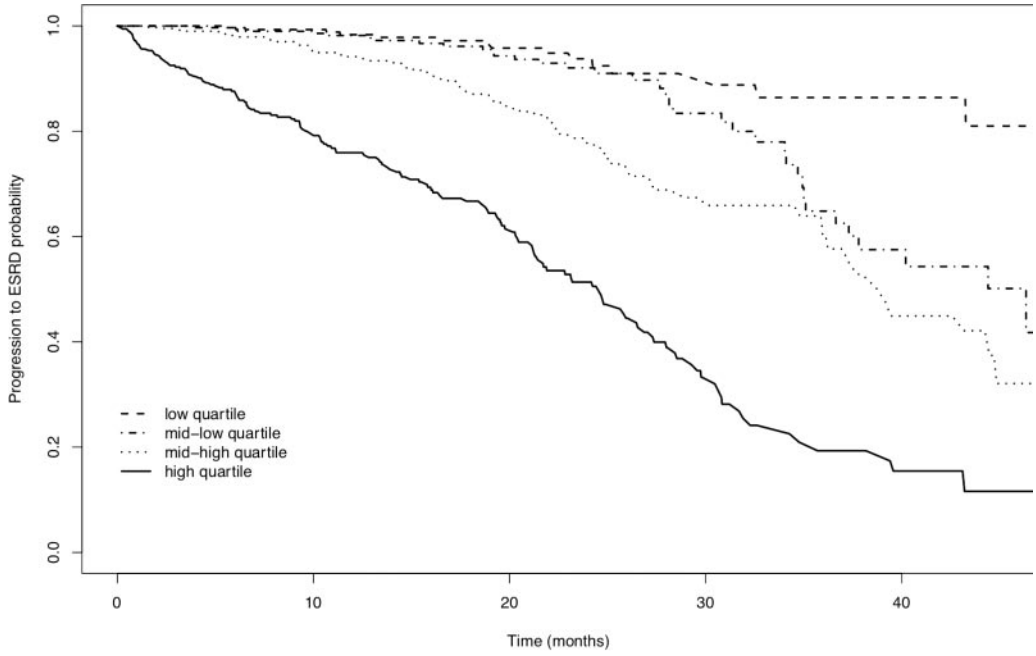

Figure 3. | Overall likelihood of progression to end-stage renal disease and dialysis inception according to the serum phosphorous quartile.

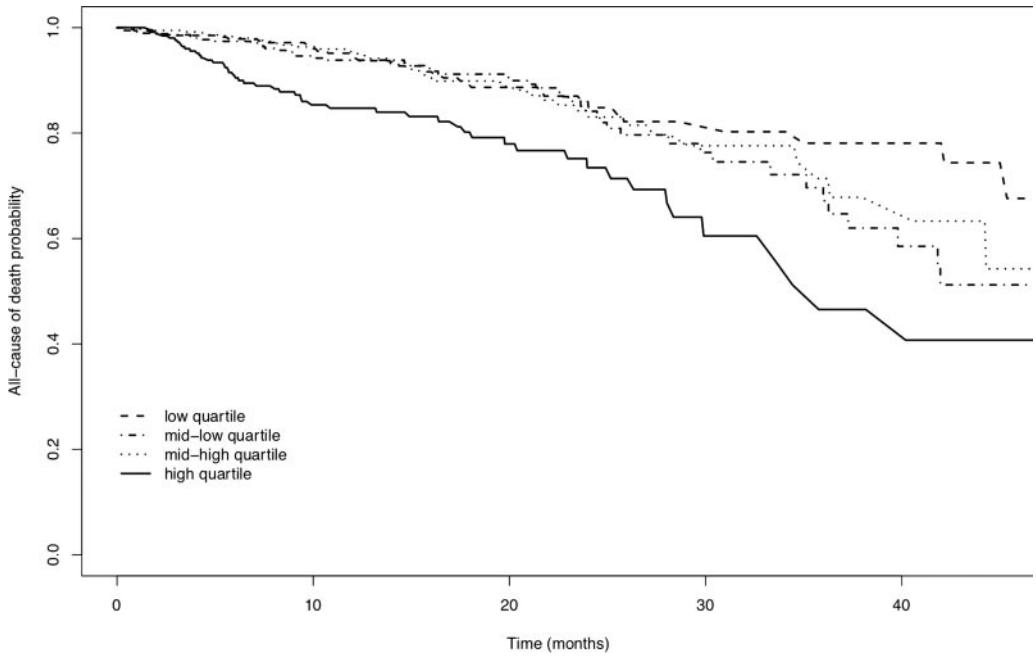

Figure 4. | Overall likelihood of all causes of death according to the serum phosphorous quartile.

yses confirmed that hyperphosphatemia predicts a rapid deterioration in residual renal function and poor prognosis in CKD patients. Our results are in line with and extend previous reports (9–14) by suggesting that the risk burden associated with hyperphosphatemia might vary in different patient subgroups.

A number of different hormones and factors interact to maintain phosphate homeostasis through the concerted action of the intestine, kidneys, and skeleton. Indeed, sex hormones, parathyroid hormone, vitamin D, and fibroblast growth factor 23 (FGF-23) and its co-receptor Klotho are probably only a few of the factors that tightly regulate intestinal absorption, incorporation in the skeleton, and/or renal excretion of phosphorus (24,25). Furthermore, if these mechanisms are thought to chronically regulate phosphorous metabolism, there is now evidence of a bowel-kidney cross talk responsible for the excretion of acutely accrued dietary phosphorus

Table 3. Predictors of the composite end point, progression to ESRD, and all-cause mortality

Variable	Composite End Point			Progression to ESRD			All-Cause Mortality		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Demographics									
age (per 1 year)	1.01	1.00 to 1.02	0.003	0.99	0.98 to 1.00	0.19	1.09	1.06 to 1.11	<0.001
men *versus* women	1.40	1.06 to 1.83	0.01	1.36	0.96 to 1.91	0.07	1.85	1.15 to 2.99	0.01
Clinical variables									
diabetes	1.20	0.93 to 1.55	0.15	1.31	0.94 to 1.84	0.10	1.41	0.93 to 2.14	0.10
hypertension	1.86	0.67 to 5.15	0.22	1.94	0.58 to 6.44	0.27	3.15	0.42 to 23.5	0.26
COPD	1.10	0.73 to 1.64	0.63	0.88	0.46 to 1.66	0.69	0.91	0.49 to 1.71	0.97
CVD	0.91	0.68 to 1.21	0.81	0.96	0.64 to 1.43	0.85	1.16	0.74 to 1.82	0.50
Laboratory variables									
serum phosphate (mg/dl)									
$P < 3.3$	0.78	0.51 to 1.19	0.25	0.61	0.30 to 1.24	0.17	0.74	0.43 to 1.28	0.29
$P \leqslant 3.3$ and < 3.8	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
$P \geq 3.8$ and < 4.3	0.93	0.66 to 1.33	0.72	1.36	0.84 to 2.18	0.20	0.64	0.36 −1.14	0.13
$P \geq 4.3$	2.04	1.44 to 2.90	<0.001	2.88	1.77 to 4.67	<0.001	2.49	1.44 to 4.32	0.001
eGFR (ml/min)	0.94	0.91 to 0.97	<0.001	0.88	0.86 to 0.91	<0.001	0.97	0.95 to 0.99	0.02
hemoglobin (>12.4 g/dl)	0.72	0.55 to 0.94	0.01	0.76	0.53 to 1.10	0.15	0.75	0.50 to 1.12	0.16
calcium (mg/dl)	0.88	0.74 to 1.04	0.15	0.75	0.61 to 0.92	0.005	1.01	0.78 to 1.31	0.90
total cholesterol (mg/dl)	0.99	0.99 to 1.00	0.40	0.99	0.99 to 1.00	0.30	1.00	0.99 to 1.00	0.99
uric acid (mg/dl)	1.01	0.99 to 1.02	0.36	1.00	0.93 to 1.08	0.86	1.00	0.99 to 1.02	0.16
Concomitant medications									
ACE inhibitor use	1.01	0.78 to 1.29	0.93	0.85	0.60 to 1.18	0.34	1.18	0.80 to 1.75	0.31
ARBs use	1.36	1.03 to 1.78	0.02	1.34	0.95 to −1.90	0.09	1.24	0.88 to 2.09	0.16
vitamin D use	1.11	0.81 to 1.50	0.49	1.39	0.96 to 2.03	0.08	1.39	0.83 to 2.93	0.20
calcium salts use	1.36	1.03 to 1.81	0.02	1.17	0.82 to 1.66	0.37	1.26	0.77 to 2.05	0.33

ARB, Angiotensin Receptor Blockers.

loads (24). Consequently, hyperphosphatemia might result from different imbalances in phosphorous metabolism.

Our findings suggest that the risk associated with a serum phosphorous level ≥4.3 mg/dl appears substantially larger in men than in women despite the fact that women tended to exhibit higher phosphate levels than men. Two previous papers have suggested similar gender heterogeneity in the association of serum phosphorus with atherosclerosis as well as with incident coronary artery disease and all-cause mortality (6,15). The reasons for such a discrepancy might be explained by the lower basal hazard in women as compared with that in men or, possibly, by the complex interplay between sex hormones and phosphorous homeostasis. Although the mechanisms are not completely understood, experimental studies have demonstrated that estrogens reduce PTH transcription and vitamin D activation as well as increase FGF-23 circulating levels (26). All of these factors contribute to regulating the renal tubular phosphate reabsorption capacity and might explain the lower phosphorous excretion observed in women than in men reported by Cirillo and co-workers (27). Furthermore, estrogen circulating levels also modulate bone turnover and calcium and phosphorous bone removal (26). Thus, renal tubular reabsorption and bone removal might account for the difference in serum phosphorous levels and for the paradoxical finding of a lower phosphorous toxicity in women as compared with that in men.

The subgroup analyses also suggest that in more advanced stages of CKD and in older age groups hyperphosphatemia might not predict renal function deterioration or death. Indeed, after adjustment for demographic, comorbidity, and laboratory factors, the association between hyperphosphatemia and risk of the composite end point was attenuated to the extent of losing statistical significance. Undeniably, these findings might be due to a selection bias in that patients prone to phosphorus toxicity do not survive CKD or die younger. Furthermore, older CKD patients are less likely than younger CKD patients to progress to ESRD, weaken the association between phosphorus and the composite end point of all causes of death, or progression to ESRD. Nevertheless, a number of biologic considerations deserve to be mentioned. Indeed, with aging, the daily dietary phosphorous intake is reduced (28) and it increases the quota of phosphorus excreted by the kidney (27). Thus, we can speculate that the accumulation of phosphorus in the body slowly diminishes throughout the lifetime (27). Thus, it is biologically plausible that the difference in the strength of the association between hyperphosphatemia and outcome in the elderly might be put down to a different phosphorous balance in the different age groups.

Finally, we detected a significant increase in phosphorous toxicity in patients with diabetes when compared with that in nondiabetic controls. Diabetes might be associated with profound and deleterious effects on parathyroid cells and osteocytes (29). In a large series of 602 CKD patients, Tanaka and co-workers have shown an independent association between diabetes and high phosphate levels as well as low PTH, FGF-23, and vitamin D levels (29). The consequent expansion of the phosphorus pool, coupled with a poor vitamin D status, might contribute to acceleration of arterial function and structure deterioration as well as explain the excessive risk of all-cause mortality associated with hyperphosphatemia in patients with diabetes (30,31).

However, this study has several limitations that ought to be pointed out. First, as PIRP is not an observational study but a collaborative network with the general practitioners, there is no study protocol. Hence, data incompleteness and lack of standardization of some biochemical parameters are the major weakness of the current results. For these reasons, PTH and vitamin D levels were not included in the analysis. However, given the complicated interplay and colinearity among these factors, we believe that adjusting for PTH and vitamin D levels might not substantially change our results. Second, aged, hypertensive CKD patients mainly constitute the study cohort and it might not be possible to generalize the results to the entire CKD population. Nonetheless, these are the patients who are currently mostly referred to nephrologists. Third, a baseline assessment does not allow for discrimination between hyperphosphatemia because of an acute or chronic impairment of phosphorous metabolism. Nevertheless, such heterogeneity should dilute the effect and bias our results toward the null. Fourth, we did not account for time-varying changes in serum phosphorus. However, considering that serum phosphorus represents only 1% of the total stores, it is unlikely that these analyses could help in determining the total amount of phosphorus in the body or the net phosphorous balance which we believe may potentially explain the modulation of the adverse effect of hyperphospatemia in different subgroups of CKD patients. Fifth, renal function was not measured but rather calculated by means of the MDRD equation; thus, a potential misclassification of CKD stages might have occurred, especially in the very old patients and more advanced stages of CKD. Finally, the observational nature of this study does not allow us to assess the causal relationship between hyperphosphatemia and poor prognosis, so future studies should assess whether serum phosphate lowering improves survival in CKD patients.

Conclusions

Our results underscore a robust association between serum phosphorus and a rapid decline in renal function and mortality. Nonetheless, subgroup analyses showed that the relative contribution of hyperphosphatemia in predicting progression to ESRD or death might differ between women, persons with diabetes, older patients, and those in more severe stages of CKD. Thus, these results suggest that the definition of hyperphosphatemia should be tailored to the individual patient group. Future studies should test whether interventions aimed at achieving different phosphorous targets improves survival in different subgroups of CKD patients.

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Disclosures

None.

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