Serum Phosphate Levels and Risk of Infection in Incident Dialysis Patients

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Background and objectives: Hyperphosphatemia is highly prevalent in dialysis patients and may be associated with immune dysfunction. The association of serum phosphate level with infection remains largely unexamined.

Design, setting, participants, & measurements: In an incident cohort of 1010 dialysis patients enrolled from 1995 to 1998 and treated in 80 US clinics, the association of phosphate level (low <3.5; normal 3.5 to 5.5; high >5.5 mg/dl) at baseline and during follow-up with the risk for incident inpatient and outpatient infection-related events was examined. Infectious events were identified from US Renal Data System data (mean follow-up 3.3 yr). Incidence rate ratios for all infections, sepsis, respiratory tract infections, and osteomyelitis were obtained using multivariable Poisson models, adjusting for potential confounders (age, race, gender, smoking, comorbidity, and laboratory values).

Results: Infections of any type (n = 1398) were more frequent among patients with high phosphate levels at baseline, relative to normal; this association was not changed by adjustment for parathyroid hormone level. Similarly, high *versus* normal baseline phosphate was associated with increased risk for sepsis and osteomyelitis but not respiratory tract infections. Associations with calcium were generally NS, and results with calcium-phosphate product mirrored the phosphate results.

Conclusions: High phosphate levels may be associated with increased risk for infection, contributing further to the rationale for aggressive management of hyperphosphatemia in dialysis patients.

Clin J Am Soc Nephrol 3: 1398–1406, 2008. doi: 10.2215/CJN.00420108

Hyperphosphatemia is highly prevalent in dialysis patients and has been targeted as an important area for improvement (1). Disorders of bone mineral metabolism, including hypo- and hyperphosphatemia, have been shown to be associated with increased risk for all-cause and cardiovascular mortality and morbidity in dialysis patients (2–5). The risk for infectious morbidity and mortality has also been shown to be increased in patients with increased phosphate levels, although this evidence is conflicting (3,5).

Patients with ESRD are known to have an increased susceptibility to infection, with diminished response to vaccination, impaired cell-mediated immunity, and reduced $CD4^+/CD8^+$ T lymphocyte ratio (6). This acquired immunity disorder concerns mainly the T lymphocytes. Although evidence is sparse, *in vivo* studies have shown that phosphate induces mitochondrial reperfusion injuries (7). More specifically, in hemodialysis patients, Yoon *et al.* (8) showed that hyperphosphatemia was directly associated with diminished populations of naive and central memory T lymphocytes. This observation may in part contribute to the acquired impaired immune response of this population, leading to an increased risk for infection.

Furthermore, hyperphosphatemia could be associated with the risk for infection in dialysis patients through other possible mechanisms. Phosphate may act purely as a surrogate for the uremic state, which has also been associated with immune dysfunction (7–13). Underlying secondary hyperparathyroidism, which results not only in abnormal phosphate levels but also elevated parathyroid hormone (PTH) levels, may contribute to infection risk (14). In a national prospective cohort study of incident dialysis patients, we examined whether serum phosphate levels at the start of dialysis and over time were associated with risk for infectious events.

Materials and Methods

Study Design

The cohort for this study, assembled from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, included 1010 incident dialysis patients who had phosphate measurements at study enrollment. These patients were treated at 80 not-for-profit dialysis clinics in 19 states throughout the United States.

Received January 24, 2008. Accepted May 5, 2008.

Published online ahead of print. Publication date available at www.cjasn.org.

Some of the data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

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ISSN: 1555-9041/305–1398

CHOICE, a national treatment effectiveness study, enrolled 1041 incident dialysis patients (767 hemodialysis, 274 peritoneal dialysis) at 81 dialysis clinics in 19 states between October 1995 and June 1998 (15). CHOICE was based on a collaborative relationship among Johns Hopkins University and Dialysis Clinics, Inc.; New Haven CAPD; and St. Raphael's Hospital. To be eligible, patients had to be ≥18 yr of age and speak either English or Spanish. Median time from dialysis initiation to enrollment was 45 d, with 98% enrolling within 4 mo of initial dialysis. Informed consent was obtained from each patient. Institutional review boards for the Johns Hopkins University School of Medicine and clinical centers approved the study protocol.

Data Collection

The independent variable in this study was serum phosphate level, measured by spectrophometric method using phosphomolybdate at enrollment (baseline, which was defined as the average of values in the 90 d surrounding study enrollment date). Because analysis of the association over the range of phosphate showed thresholds similar to the current clinical guidelines, we chose to categorize the variable into three categories on the basis of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines (1): <3.5 mg/dl ("low"), >5.5 mg/dl ("high"), and 3.5 to 5.5 mg/dl (target range). We also examined serum phosphate level as a continuous variable to determine the effect per 1 mg/dl greater phosphate.

The primary outcome was the count of nonfatal infectious events. US Renal Data System inpatient and outpatient files were used; dialysis, home health, and skilled nursing facility files were excluded, because these events were less likely to be independent events (16). Primary billing codes were used to exclude nosocomial or hospital-acquired infections. Any outpatient event that was between 30 d before an inpatient admission and 30 d after an inpatient discharge for the same category of infectious event was considered the same event; inpatient admissions that were within 30 d of discharge for a previous admission for the same category of infection were also considered the same event.

Both all infectious events and individual categories of infectious episodes served as outcomes. The *International Classification of Diseases, Ninth Revision* codes used were sepsis (038.x [septicemia] or 790.7 [bacteremia]), respiratory tract infections (461.x [sinusitis], 462 [pharyngitis], 465.x [upper respiratory infection], 466.x [bronchitis], 473.x [chronic sinusitis], 480.x [viral pneumonia], 481 [pneumococcal pneumonia], 482.x [other bacterial pneumonia], 485 [bronchopneumonia, unspecified], 486 [pneumonia, unspecified], 487.x [influenza], 490 [bronchitis, not otherwise specified], or 513.x [abscess of lung and mediastinum]), osteomyelitis (730.x [osteomyelitis, periostitis, and other bone infections]), gastrointestinal infections (003.x [*Salmonella* infections], 007.x [protozoal infections], 008.x [intestinal infections due to other organisms], 009.x [ill-defined intestinal infections], or 567.X [peritonitis]), central nervous system infections (036.x [meningococcal infection], 047.x [meningitis due to enterovirus], 049.x [other viral diseases of the nervous system], 320.x [bacterial meningitis], or 324.x [intracranial and intraspinal abscess]), fungal infections (112.x [candidiasis] or 117.x [other mycoses]), skin infections (680.x [carbuncle and furuncle], 681.x [cellulitis and abscess of finger and toe], 682.x [other cellulitis and abscess], 684 [impetigo], 686.x [other local infection of skin], or 729.3x [panniculitis, unspecified]), septic arthritis (711.x [arthropathy associated with infections] or 996.66/996.67 [infection due to internal prosthetic, implant, and graft]), and access-related infections (996.62 [infection due to vascular access]) (17).

We also examined data on demographic, laboratory, and clinical characteristics. Data on age, gender, race, employment, and smoking status were collected from a baseline self-report questionnaire. Laboratory values and height and weight (used to calculate body mass index [BMI]) were obtained from clinic records and from the Centers for Medicare and Medicaid Services Medical Evidence report (CMS Form 2728). Dialysis modality at baseline was defined as the modality at 4 wk after study enrollment. Comorbidity was assessed at baseline by abstraction of dialysis unit records, hospital discharge summaries, medication lists, consultation notes, diagnostic imaging, and cardiac imaging reports and scoring of the Index of Coexistent Disease by two trained nurses. The Index of Coexistent Disease provides a composite integer score ranging from 0 to 3 (with 3 being the highest severity level) and is a measure of both the presence and the severity of comorbid conditions (18–21). History of diabetes and cardiovascular disease were also determined by this process. Late referral was defined as a first visit to a nephrologist <4 mo before start of dialysis (22). US Renal Data System medical evidence and claims data were used to assess injectable vitamin D (calcitriol) use. Hemodialysis dosage (Kt/V) was calculated from values of blood urea nitrogen, pre- and postdialysis weight, and dialysis duration using the Daugirdas formula (23). Information on vascular access for hemodialysis patients was compiled from a review of discharge summaries, dialysis flow sheets, and dialysis clinic progress notes (24). Laboratory values, including phosphate, calcium, albumin, creatinine, and hemoglobin, were obtained from monthly laboratory testing; baseline laboratory values were defined as the average of values in the 90 d surrounding study enrollment date. High-sensitivity C-reactive protein values were measured in special study-related blood draws (25). PTH levels were determined for some patients through routine clinical care (Diasorin assay). All calcium levels were corrected for albumin [corrected calcium = calcium level + 0.8*(4 − albumin level)]. Baseline statin use (26) and nonadherence to dialysis sessions (27), defined as missing >3% of sessions, were as described previously.

Statistical Analyses

We first compared patient characteristics by baseline level of serum phosphate (<3.5, 3.5 to 5.5, and >5.5 mg/dl) using Pearson χ^2 tests for categorical variables and ANOVA for continuous variables. Crude incidence rates of infection were calculated by dividing the number of events by the cumulative time at risk for each group. Time at risk for infectious events started with study enrollment or the Medicare eligibility date, if the patient was not Medicare-eligible at the start of the study, and continued through December 31, 2004. Time during hospitalization was excluded from time at risk. Patients were censored at death or kidney transplantation.

Multivariable Poisson regression models were used to obtain incidence rate ratios (IRR) for high and low levels of phosphate, adjusted for potential cofounders. Variables were considered for inclusion in multivariable regression models on the basis of evidence that they were confounders (*i.e.*, significant association with both phosphate level and infectious events) or because of previous evidence of their association with either of the dependent or independent variable. We accounted for possible dependence of observations within clinics (28) by performing fixed-effects modeling clustered on the dialysis clinic. All analyses were performed using Stata 9.2 (Stata Corp., College Station, TX), and the threshold for statistical significance was set at $P < 0.05$.

Finally, we performed several sensitivity analyses. We limited our examination of phosphate to hemodialysis patients only and also analyzed calcium and calcium-phosphate product levels as independent variables. We also looked at results without the patients ($n = 9$) whose

Medicare eligibility dates did not precede their study enrollment. The effect of including fatal events ($n = 64$) was also examined. We examined the association with the inclusion of hospital-acquired infections (*i.e.*, including secondary infection codes). Finally, we performed time-to-event analyses, with infections treated as multiple failures.

Results

Patient Characteristics by Baseline Phosphate Level

Table 1 shows the patient characteristics of the study cohort by baseline phosphate level. Patients who were younger, male, white, or employed; who smoked; who were on hemodialysis (*versus* peritoneal dialysis); who had fewer and less severe comorbidities; and who were referred to a nephrologist >4 mo before they started dialysis all were more likely to have higher phosphate levels. Mean Kt/V (in hemodialysis patients only) and hemoglobin were lower with higher phosphate level, while mean creatinine and median PTH were higher with higher phosphate level. Phosphate level did not differ in a statistically significantly manner by any other patient characteristic examined.

Association of Baseline Phosphate Level with Infection

There were a total of 1398 nonfatal infectious events during study follow-up. Having high (>5.5 mg/dl) phosphate at baseline was associated with increased infection, whereas low (<3.5 mg/dl) baseline phosphate was associated with decreased infection (Table 2). The association of high phosphate with increased risk for infection persisted with adjustment for demographic, clinical, and laboratory variables, whereas the association of low phosphate with decreased risk became statistically significant only with adjustment. When only sepsis

Table 1. Patient characteristics by baseline phosphate level[a]

Characteristic	*N*	Phosphate Level (mg/dl)			*P*[b]
		<3.5	3.5 to 5.5	>5.5	
Total	1010	74 (7.3%)	559 (55.4%)	377 (37.3%)	
Demographic					
age (yr; mean [SD])	1010	64.4 (15.1)	59.8 (14.7)	53.8 (14.3)	<0.001
gender (% female)	1010	60.8	46.0	43.2	0.021
race (% white)	1010	56.8	67.4	69.0	0.049
employment (% working)	1009	2.7	13.4	14.9	0.008
Clinical					
dialysis modality (% hemodialysis)	1010	66.2	72.5	78.3	0.037
smoking status (% ever smoker)	951	56.1	57.4	65.8	0.031
ICED score (%)	1008				
≤1		27.4	36.0	36.1	0.031
2		26.0	34.8	36.1	
3		46.6	29.2	27.9	
diabetes (% diabetic)	1008	57.5	52.7	57.0	0.373
history of CVD (% positive)	1007	53.4	45.3	41.0	0.110
late referral (% <4 mo)	807	36.5	32.3	25.0	0.052
BMI (kg/m^2; mean [SD])	947	27.4 (8.2)	26.8 (6.5)	27.4 (6.7)	0.347
Kt/V (mean [SD])[c]	582	1.35 (0.32)	1.29 (0.29)	1.22 (0.30)	0.003
baseline access (% catheter)[c]	508	64.7	68.5	63.7	0.536
statin use (%)	1010	14.9	14.0	13.3	0.917
vitamin D use (%)	424	17.5	10.5	18.6	0.068
nonadherence (%)	728	4.4	7.9	11.7	0.126
Laboratory					
albumin (g/dl; mean [SD])	1006	3.56 (0.30)	3.62 (0.38)	3.63 (0.38)	0.309
calcium (mg/dl; mean [SD])	1009	8.99 (0.64)	9.09 (0.66)	9.02 (0.80)	0.245
hemoglobin (g/dl; mean [SD])	1001	11.1 (1.4)	10.8 (1.3)	10.7 (1.3)	0.036
creatinine (g/dl; mean [SD])	1005	6.07 (2.47)	6.69 (2.14)	8.31 (2.70)	<0.001
CRP (mg/dl; median [IQR])	856	0.5 (0.3 to 1.5)	0.4 (0.2 to 0.7)	0.4 (0.2 to 1.1)	0.282
PTH (pg/ml; median [IQR])	665	125 (63 to 243)	151 (69 to 291)	176 (86 to 361)	0.044

[a]BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; ICED, Index of Coexistent Disease; IQR, interquartile range; PTH, parathyroid hormone.
[b]By Pearson χ^2 or ANOVA.
[c]Hemodialysis patients only.

Table 2. Incidence rates and adjusted IRR for infectious events by baseline phosphate level[a]

Type of Infection	Incidence Rate, Per 1000 Patient-Years	IRR (95% CI)			
		Unadjusted	+Demographics	+Clinical	+Laboratory
All (mg/dl)		$n = 1008$[b]	$n = 1008$	$n = 947$	$n = 935$
<3.5	314	0.91 (0.71 to 1.16)	0.88 (0.69 to 1.13)	0.72 (0.55 to 0.96)[c]	0.61 (0.46 to 0.82)[c]
3.5 to 5.5	399	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>5.5	480	1.19 (1.06 to 1.33)[c]	1.24 (1.10 to 1.39)[c]	1.22 (1.09 to 1.38)[c]	1.28 (1.12 to 1.45)[c]
P for trend		0.003[c]	0.001[c]	0.002[c]	0.001[c]
Sepsis (mg/dl)		$n = 972$[b]	$n = 972$	$n = 911$	$n = 902$
<3.5	29	0.67 (0.31 to 1.46)	0.62 (0.29 to 1.36)	0.61 (0.28 to 1.34)	0.61 (0.28 to 1.36)
3.5 to 5.5	73	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>5.5	86	1.14 (0.88 to 1.48)	1.29 (0.98 to 1.70)	1.39 (1.05 to 1.85)[c]	1.44 (1.07 to 1.95)[c]
P for trend		0.344	0.083	0.032[c]	0.027[c]
Respiratory tract (mg/dl)		$n = 995$[b]	$n = 995$	$n = 928$	$n = 916$
<3.5	94	0.90 (0.58 to 1.40)	0.88 (0.56 to 1.37)	0.80 (0.49 to 1.31)	0.81 (0.49 to 1.32)
3.5 to 5.5	116	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>5.5	124	1.03 (0.83 to 1.28)	1.12 (0.90 to 1.40)	1.05 (0.84 to 1.32)	1.08 (0.85 to 1.38)
P for trend		0.796	0.332	0.750	0.599
Osteomyelitis (mg/dl)		$n = 809$[b]	$n = 809$	$n = 758$	$n = 749$
<3.5	8	0.46 (0.10 to 1.96)	0.46 (0.11 to 1.94)	[d]	[d]
3.5 to 5.5	21	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>5.5	34	1.59 (1.02 to 2.48)[c]	1.73 (1.09 to 2.75)[c]	1.68 (1.04 to 2.72)[c]	1.73 (1.05 to 2.86)[c]
P for trend		0.046[c]	0.029[c]	0.065	0.081

[a]Demographics: age, gender, race; clinical: modality, ICED, smoking status; laboratory: albumin, creatinine, hemoglobin. Total number of nonfatal infections was 1398; sepsis infections, 246; respiratory tract infections, 389; osteomyelitis, 82. CI, confidence interval.
[b]Observations in groups with no variation in outcome dropped in conditional modeling.
[c]$P < 0.05$.
[d]No estimate because of small cell sizes.

events were examined, high phosphate was associated with increased risk but only with adjustment. High phosphate was associated with increased risk for respiratory tract infections, but the associations were not statistically significant. High phosphate was associated with increased incidence of osteomyelitis, regardless of adjustment. Other types of infections (*e.g.*, gastrointestinal, fungal, access-related, skin) generally did not show statistically significant associations with phosphate level. When phosphate was examined as a continuous variable, each 1 mg/dl greater phosphate was associated with increased risk for all infections (IRR 1.10; 95% confidence interval [CI] 1.05 to 1.16), sepsis (IRR 1.12; 95% CI 0.99 to 1.26), and osteomyelitis (IRR 1.26; 95% CI 1.02 to 1.56) after adjustment for demographics and clinical and laboratory variables.

These results were robust to further adjustment for either vitamin D use (for all infections, high phosphate IRR 1.42 [95% CI 1.19 to 1.70]; low phosphate IRR 0.57 [95% CI 0.39 to 0.82]) or PTH (high phosphate IRR 1.50 [95% CI, 1.28 to 1.75]; low phosphate IRR 0.80 [95% CI 0.54 to 1.18]). Adjustment for statin use, late referral to a nephrologist, BMI, and nonadherence to dialysis also did not affect the results for either all infections or infection subtypes (data not shown).

Risk for respiratory tract infections and osteomyelitis did not differ by age, race, or diabetic status; however, the increased risks for infection with high phosphate were seen only in the younger (<65 yr) patients; the protective effects of low phosphate were seen only in the older patients (Table 3). In addition, white patients with high phosphate were at higher risk for infection, but the interaction with race was NS ($P_{interaction} = 0.799$). Patients with diabetes and low phosphate were at lower risk than similar patients without diabetes for all infections ($P_{interaction} = 0.040$). Generally, associations between phosphate and all infections were similar across BMI and creatinine subgroups. For those with albumin levels <3.7 g/dl, low phosphate was not associated with increased risk, but those with higher levels did show an increased risk for infection ($P_{interaction} = 0.013$). For those with dialysis dose <1.3, high phosphate was not associated with increased risk, but those with higher doses did show an increased risk for infection ($P_{interaction} = 0.009$).

Sensitivity Analyses

In sensitivity analyses, we examined the effect of baseline vascular access type (catheter *versus* fistula/graft) and dialysis dose (Kt/V) in hemodialysis patients only (Table 4). In general,

Table 3. Adjusted IRR for all infectious events for subgroups of patients by baseline phosphate level

Subgroup[a]	IRR (95% CI) *versus* 3.5 to 5.5 mg/dl[b]	
	<3.5 mg/dl	>5.5 mg/dl
Age (yr)		
<65 (n = 601)	0.90 (0.60 to 1.35)	1.43 (1.21 to 1.68)[c]
≥65 (n = 329)	0.47 (0.30 to 0.74)[c]	0.95 (0.75 to 1.21)
$P_{interaction}$	0.010[c]	0.008[c]
Race		
white (n = 619)	0.63 (0.40 to 1.00)	1.25 (1.05 to 1.47)[c]
black (n = 257)	0.49 (0.32 to 0.74)[c]	1.02 (0.78 to 1.32)
$P_{interaction}$	0.805	0.799
Diabetic status		
nondiabetic (n = 424)	0.83 (0.55 to 1.25)	1.51 (1.20 to 1.89)[c]
diabetic (n = 499)	0.44 (0.30 to 0.71)[c]	1.18 (1.00 to 1.40)[c]
$P_{interaction}$	0.040[c]	0.422
BMI (kg/m^2)		
<25 (n = 366)	0.72 (0.52 to 0.99)[c]	1.29 (1.09 to 1.53)[c]
≥25 (n = 490)	0.84 (0.64 to 1.11)	1.23 (1.08 to 1.39)[c]
$P_{interaction}$	0.245	0.791
Albumin (g/dl)		
<3.7 (n = 482)	0.89 (0.70 to 1.13)	1.29 (1.14 to 1.47)[c]
≥3.7 (n = 447)	0.46 (0.32 to 0.67)[c]	1.22 (1.05 to 1.40)[c]
$P_{interaction}$	0.013[c]	0.369
Creatinine (g/dl)		
<7.0 (n = 469)	0.56 (0.42 to 0.74)[c]	1.46 (1.28 to 1.66)[c]
≥7.0 (n = 459)	1.61 (1.21 to 2.14)[c]	1.17 (1.03 to 1.33)[c]
$P_{interaction}$	0.317	0.732
Dialysis dose (hemodialysis only)		
Kt/V <1.3 (n = 308)	1.08 (0.77 to 1.51)	0.98 (0.83 to 1.16)
Kt/V ≥1.3 (n = 245)	0.88 (0.56 to 1.38)	1.49 (1.23 to 1.80)[c]
$P_{interaction}$	0.270	0.009[c]

[a]Observations in groups with no variation in outcome dropped in conditional modeling.
[b]Adjusted for demographics (age, gender, race), clinical (modality, ICED, smoking status), and laboratory (albumin, creatinine, hemoglobin).
[c]$P < 0.05$.

patterns of association, with high phosphate being associated with greater incidence of overall infection, were similar in hemodialysis patients, compared with the overall cohort. Adjustment for access type did not affect the associations of low and high phosphate with all infections; adjustment for dialysis dose resulted in a loss of statistical significance; however, adjustment for access type diminished the association between high phosphate and osteomyelitis (IRR 1.05; 95% CI 0.55 to

Table 4. Adjusted IRR for all infectious events by baseline phosphate level in hemodialysis patients only

Phosphate Level (mg/dl)	IRR (95% CI)			
	Adjusted[a] (n = 739)[b]	+Access Type (n = 504)	+Dialysis Dose (n = 578)	+Both (n = 393)
<3.5	0.87 (0.64 to 1.19)	0.83 (0.57 to 1.21)	1.21 (0.87 to 1.68)	1.13 (0.76 to 1.70)
3.5 to 5.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>5.5	1.22 (1.07 to 1.39)[c]	1.27 (1.08 to 1.50)[c]	1.11 (0.95 to 1.29)	1.12 (0.93 to 1.35)
P for trend	0.005[c]	0.004[c]	0.180	0.224

[a]Adjusted for age, race, ICED, and albumin.
[b]Observations in groups with no variation in outcome dropped in conditional modeling.
[c]$P < 0.05$.

2.02), and dialysis dose did the same for sepsis (IRR 0.86; 95% CI 0.61 to 1.22).

The associations of infections with both baseline calcium and calcium-phosphate product were also examined. There was no significant adjusted association between infection and either high calcium (>9.5 mg/dl IRR 1.01; 95% CI 0.90 to 1.14) or low calcium (<8.4 mg/dl IRR 1.07; 95% CI 0.80 to 1.41), compared with K/DOQI target range. This was consistent for infection subtypes, except sepsis (>9.5 mg/dl IRR 1.59 [95% CI 0.89 to 2.85]; <8.4 mg/dl IRR 1.45 [95% CI 1.09 to 1.92]). The results with calcium-phosphate product generally mirrored those with phosphate alone, with high product ($\geq$55 mg^2/dl^2) being associated with higher risk for all infection, sepsis, and osteomyelitis (Table 5). In hemodialysis patients only, adjustment for access type did not change the association of calcium-phosphate product with all infections (IRR 1.34; 95% CI 1.13 to 1.59), but adjustment for dialysis dosage did result in a loss of statistical significance (IRR 1.13; 95% CI 0.96 to 1.33).

The exclusion of the nine patients who were not Medicare-eligible at study enrollment gave results that were nearly identical to those that included these patients. For all infections, the results for high and low phosphate were as follows: IRR 1.28 (95% CI 1.13 to 1.46) and IRR 0.61 (95% CI 0.46 to 0.82), respectively. For sepsis, the same results were as follows: IRR 1.47 (95% CI 1.09 to 1.98) and IRR 0.62 (95% CI 0.28 to 1.37), respectively; for osteomyelitis, IRR 1.82 (95% CI 1.09 to 3.04) for high phosphate. The effect of adding the 64 fatal infections was minimal for all infections, with results for high and low phosphate being IRR 1.29 (95% CI 1.13 to 1.46) and IRR 0.66 (95% CI 0.50 to 0.87), respectively. Similar minimal changes were seen with sepsis, respiratory tract, and osteomyelitis infections. The inclusion of hospital-acquired infections gave similar results, with associations for high and low phosphate as follows: All infections IRR 1.26 (95% CI 1.15 to 1.38) and IRR 0.70 (95% CI 0.57 to 0.85); sepsis IRR 1.52 (95% CI 1.25 to 1.85) and IRR 0.58 (95% CI 0.35 to 0.96); respiratory tract infections IRR 1.05 (95% CI 0.87 to 1.27) and IRR 0.61 (95% CI 0.40 to 0.93); and osteomyelitis IRR 1.42 (95% CI 0.98 to 2.05) and IRR 0.15 (95% CI 0.04 to 0.65).

When infections were modeled as multiple time-to-event failures, results were similar for high phosphate (all infections: relative hazard [RH] 2.00 [95% CI 1.36 to 2.94]; sepsis infections: RH 3.24 [95% CI 1.16 to 9.06]); however, in these models, low phosphate was also associated with increased risk for infection (all infections: RH 1.70 [95% CI 1.18 to 2.44]; sepsis infections: RH 2.51 [95% CI 0.92 to 6.84]). The addition of a covariate indicating previous infection did not change the associations of phosphate with infection, but, not surprisingly, the presence of a previous infection was itself associated with much higher risk for infection (all infections: RH 2.65 [95% CI 2.32 to 3.02]; sepsis infections: RH 4.86 [95% CI 3.31 to 7.15]).

Discussion

In this national prospective cohort study, we found that high levels of phosphate early after the start of dialysis were associated with increased risk for subsequent infection. This association was consistent for various subtypes of infection. Adjustment for vitamin D use, PTH levels, vascular access type, and dialysis dose did not affect the association of phosphate with all infections. The association was also not explained by calcium

Table 5. Adjusted IRR for infectious events by baseline calcium-phosphate product level[a]

Type of Infection	IRR (95% CI)			
	Unadjusted	+Demographics	+Clinical	+Laboratory
All (mg^2/dl^2)	$n = 1003$[b]	$n = 1003$	$n = 944$	$n = 935$
<55	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥55	1.22 (1.08 to 1.37)[c]	1.26 (1.11 to 1.42)[c]	1.27 (1.12 to 1.45)[c]	1.38 (1.21 to 1.59)[c]
P for trend	0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]
Sepsis	$n = 967$[b]	$n = 967$	$n = 908$	$n = 902$
<55	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥55	1.40 (1.07 to 1.82)[c]	1.67 (1.26 to 2.21)[c]	1.76 (1.31 to 2.36)[c]	1.87 (1.36 to 2.57)[c]
P for trend	0.014[c]	<0.001[c]	<0.001[c]	<0.001[c]
Pulmonary	$n = 990$[b]	$n = 990$	$n = 925$	$n = 916$
<55	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥55	0.99 (0.79 to 1.25)	1.08 (0.85 to 1.36)	1.06 (0.82 to 1.35)	1.06 (0.82 to 1.38)
P for trend	0.963	0.551	0.670	0.648
Osteomyelitis	$n = 804$[b]	$n = 804$	$n = 755$	$n = 749$
<55	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥55	1.66 (1.05 to 2.62)[c]	1.63 (1.01 to 2.64)[c]	1.65 (0.98 to 2.79)	1.78 (1.01 to 3.14)[c]
P for trend	0.029[c]	0.045[c]	0.060	0.047[c]

[a]Demographics: age, gender, race; clinical: modality, ICED, smoking status; laboratory: albumin, creatinine, hemoglobin. Calcium levels corrected for albumin level.
[b]Observations in groups with no variation in outcome dropped in conditional modeling.
[c]$P < 0.05$.

levels. There was some evidence that low phosphate levels were associated with decreased risk for infection, but these results were not as robust to adjustment.

The pathophysiologic mechanisms by which hyperphosphatemia could increase the susceptibility of dialysis patients to infection are not well established. To our knowledge, there are very few reports (8) on the direct effects of high extracellular phosphate concentrations on the functions of cells involved in the protection of humans or experimental animals from pathogenic organisms. Nevertheless, a direct adverse effect cannot be excluded. Alternatively, hyperphosphatemia might have an indirect effect as a result of its role in the development of secondary hyperparathyroidism, or it may act as a surrogate of inadequate dialysis dose.

The argument could be made that increased phosphate level is a marker of secondary hyperparathyroidism and that this condition, rather than phosphate alone, results in dialysis patients' increased susceptibility to infection. Although it has been postulated that the mechanism of immunomodulation as a result of secondary hyperparathyroidism is through PTH (14,29,30) or vitamin D (31) levels, we found no difference in our main results when we adjusted for PTH and vitamin D use. It should be noted that our study predates the widespread use of newer vitamin D agents (doxercalciferol and paricalcitol), according to opinion-based guidelines for vitamin D levels in dialysis patients; however, a recent meta-analysis showed that the association of vitamin D use with improved health outcomes in patients with kidney disease remains controversial (32,33).

Hyperphosphatemia in hemodialysis patients could also be a reflection of inadequate dialysis dosage, which could, in turn, lead to increased risk for infection; however, we found that adjustment for dialysis dosage, although rendering the results nonstatistically significant, did not reverse the positive direction of the association. Also, stratified analyses showed that even in the setting of adequate dialysis, increased phosphate is still associated with increased risk for infection, arguing that phosphate's effect is independent of dialysis dosage. Thus, it seems that the association between phosphate and risk for infection may be only partially driven by poor dialysis and uremia, of which phosphate is a possible marker (11). Hemodialysis patients who use a catheter for vascular access are also at increased risk for infection relative to those who use arteriovenous fistulas or grafts (34,35). In our study, adjustment for access type did not affect the results substantially, except for diminishing the association between phosphate and osteomyelitis. The risk associated with low phosphate could indicate that decreased phosphate reflects poor nutritional status, which in turn may increase infection risk (36); however, our stratified results suggest that phosphate has an effect independent of nutritional status.

Time-to-event analyses showed that not only high but also low phosphate was associated with greater risk for infection. This difference in results may be due to differences in modeling. That is, our main analyses modeled the number of hospitalizations over follow-up whereas the time-to-event analyses modeled the amount of time before hospitalization. It may be that patients who had low phosphate at baseline, who were possibly malnourished, were more likely to have an acute infection just after the start of dialysis than those with normal phosphate, thus leading to higher RH; however, these same patients may have had fewer infections over the course of dialysis, leading to a lower relative risk for hospitalization.

This study is subject to several limitations. The use of primary discharge codes, although excluding misclassifications of outcomes as a result of facility-acquired infections, may have resulted in underdetection of infectious events. Although we were able to look at several types of infection, to gain power, we aggregated many types of infection (skin, osteoarthritis, access, and gastrointestinal infections, in addition to sepsis, respiratory tract infections, and osteomyelitis) to look at all infections. This grouping may have masked specific effects of phosphate in infection subtypes if the associations were of differing directions or magnitudes. Data on several factors of interest, including dialysis dose, vitamin D use, and PTH levels, were not available for all patients in the study, and there may be biases in who had available measurements. Vitamin D levels were not available on any of the patients. Because this was an observational study, there is a risk for confounding, despite our attempts to adjust for factors that we considered to be the most important confounders. The potential for residual bias as a result of unknown or unmeasured factors cannot be excluded.

Conclusions

This national prospective cohort study found that high levels of phosphate early in the course of dialysis were associated with increased risk for subsequent infection. This association was not explained by evidence of secondary hyperparathyroidism or uremia as a result of poor dialysis, suggesting that phosphate may be an independent risk factor for infection. These results are consistent with the call for better hyperphosphatemia management in dialysis patients (1,37). Confirmation of these results in larger prospective cohorts would further suggest that more aggressive management of hyperphosphatemia in dialysis patients could result in decreased infectious morbidity among dialysis patients.

Acknowledgments

This work was supported by grant RO1 DK 59616 from the National Institute of Diabetes and Digestive and Kidney Diseases; grant R01-HS-08365 from the Agency for Health Care Research and Quality; and grant R01 HL 62985 from the National Heart, Lung, and Blood Institute. N.R.P. is supported by grant K24DK02643 and M.L.M. is supported by grant K23DK078774 from the National Institute of Diabetes and Digestive and Kidney Diseases.

We thank the patients, staff, laboratory, and medical directors of the participating clinics at DCI, St. Raphael's Hospital, and New Haven CAPD who contributed to the study.

This study was presented in part at the annual meeting of the American Society of Nephrology; November 2 through 5, 2007; San Francisco, CA.

Disclosures

None.

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