Calcium, Phosphorus, Parathyroid Hormone, and Cardiovascular Disease in Hemodialysis Patients: The USRDS Waves 1, 3, and 4 Study

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Animal studies suggest that calcium-phosphorus homeostatic abnormalities cause cardiovascular disease in uremia; few observational studies in humans have explored this. Associations in the retrospective United States Renal Data System Waves 1, 3, and 4 Study of 14,829 patients who were on hemodialysis on December 31, 1993, were examined. Mean age and duration of renal replacement therapy were 60.0 and 3.2 yr, respectively; 40.7% had diabetes. Quintiles (Q_1 to Q_5) of (albumin-adjusted) calcium were ≤8.7, 8.8 to 9.2, 9.3 to 9.6, 9.7 to 10.2, and >10.2 mg/dl; phosphorus, ≤4.4, 4.5 to 5.3, 5.4 to 6.3, 6.4 to 7.5, and >7.5 mg/dl; calcium-phosphorus product, ≤40.9, 41.0 to 50.1, 50.2 to 59.2, 59.3 to 71.0, and >71.0 mg^2/dl^2; and parathyroid hormone (PTH), ≤37, 38 to 99, 100 to 210, 211 to 480, and >480 pg/ml. Higher calcium levels were associated with fatal or nonfatal cardiovascular events (adjusted hazards ratio, 1.08 for Q_5, *versus* Q_1) and all-cause mortality (Q_2, 1.07; Q_4, 1.11; Q_5, 1.14). Phosphorus levels were associated with cardiovascular events (Q_2, 1.06; Q_3, 1.13; Q_4, 1.14; Q_5, 1.25) and mortality (Q_4, 1.10; Q_5, 1.19), calcium-phosphorus product was associated with cardiovascular events (Q_3, 1.09; Q_4, 1.14; Q_5, 1.24) and mortality (Q_4, 1.09; Q_5, 1.19), and PTH levels were associated with cardiovascular events (Q_5, 1.12) and mortality (Q_5, 1.17). Despite limitations (including retrospective design; noncurrent study era; and lack of serial calcium, phosphorus, and PTH measurements), this study suggests that disorders of calcium homeostasis are associated with fatal and nonfatal cardiovascular events and all-cause mortality in hemodialysis patients.

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A link between secondary hyperparathyroidism and cardiovascular disease in dialysis patients has been suspected for decades (1–3). As in other types of cell, high levels of parathyroid hormone (PTH) seem to damage cardiac myocytes, possibly through a calcium ionophore effect (4). Animal models have convincingly demonstrated that PTH is a "permissive" factor in the development of uremic cardiomyopathy (5). Some studies have shown left ventricular function and size to be improved after parathyroidectomy (2,6).

The hypothesis that calcium and phosphorus deposition may have direct cardiovascular consequences, independent of PTH levels, also has been a matter of speculation for many years (1). The possibility that the deposition of calcium and phosphorus causes vascular disease in ESRD has been the focus of much recent research. Morphologic studies, for example, suggest that calcium deposition in blood vessels is a dynamic process (7,8). Coronary artery calcification is highly prevalent and rapidly progressive in hemodialysis patients (9,10). High calcium-phosphorus products and PTH levels have been associated with overall mortality and mortality attributed to cardiovascular disease in hemodialysis patients (11,12). A calcium-free oral phosphorus binder, sevelamer, has been found to reduce the rate of progression of coronary artery calcification in hemodialysis patients, as compared with calcium-containing binders (13).

To date, few studies have systematically investigated potential associations of calcium, phosphorus, and PTH levels with specific cardiovascular events. This study is an attempt to investigate such associations. The objectives of this study were to investigate associations between candidate variables:

1. (albumin-adjusted) serum calcium,
2. serum phosphorus,
3. calcium-phosphorus product, and
4. PTH levels

and the following outcomes in hemodialysis patients:

1. The primary outcome was the first nonfatal or fatal cardiovascular event, henceforth referred to as "cardiovascular events." A nonfatal cardiovascular event was defined as hospitalization with ischemic heart disease, congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease. A fatal cardiovascular event was defined as cause of death categorized on the ESRD Death Notification Form as acute myocardial infarction, hyperkalemia, pericarditis (including cardiac tamponade), atherosclerotic heart

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disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest of unknown cause, valvular heart disease, pulmonary edema as a result of exogenous fluid, cerebrovascular accident (including intracranial hemorrhage), or ischemic brain damage.
2. All-cause mortality also was evaluated.

Materials and Methods

Patients and Baseline Measurements

We used the Waves 1, 3, and 4 Dialysis Morbidity and Mortality Study, a historical cohort study of dialysis patients in the United States. More than 1300 dialysis units were randomly selected throughout the United States, and data were collected on one of every five patients who were alive on December 31, 1993. Data abstraction began in 1995 and continued for 3 yr. The original database included 16,733 subjects. For this study, which relied on the use of patients' unique United States Renal Data System identification numbers to link data sets, our major exclusion criteria were the absence of this identifier ($n = 1751$) and duplicate use of the same identifier ($n = 7$). Other exclusion criteria were the absence of a date of birth ($n = 98$) and a date of death that preceded the study start date ($n = 48$). The final sample size was 14,829. Predialysis laboratory variables were used. For calcium, phosphorus, hemoglobin, and creatinine, a single value from December 1993 was recorded; a value from November 1993 was recorded when values from December 1993 were not available. Calcium was corrected for serum albumin levels <4.0 g/dl as follows: Corrected calcium = calcium + $0.8 \times (4 -$ serum albumin) (14,15). For PTH and serum albumin, the most recent value between July 1993 and December 1993 was used.

Outcomes

Patients were followed from January 1, 1994, until December 31, 2001. *International Classification of Diseases, Ninth Revision, Clinical Modification* codes were used to define cardiovascular events from the Part A Medicare inpatient claims file. The following codes were used: (*1*) ischemic heart disease, 410.xx, 411.x, 411.8, 413.x, and 414.x; (*2*) congestive heart failure, 428.xx; (*3*) stroke or transient ischemic attack, 431, 433.xx, 434.xx, 435, 436, and 437.0; and (*4*) peripheral vascular disease, 440.x. We used the United States Renal Data System Patients File to obtain dates of death and renal transplantation. Causes of death were obtained from the ESRD Death Notification Form.

Statistical Analyses

Calcium, phosphorus, calcium-phosphorus product, and PTH levels were handled in quintiles. In addition, serum calcium, phosphorus, and PTH levels were dichotomized into high and low categories to analyze the interaction among the three parameters, cardiovascular events, and death. Serum calcium levels were dichotomized as ≥10.2 mg/dl, serum phosphorus as ≥5.5 mg/dl, and serum PTH as ≥408 pg/ml (the mean PTH value in our study population). Cox regression was used to study event-free survival times, with adjustment made for baseline demographic characteristics, comorbidity, measures of hemodialysis adequacy, serum albumin level, body mass index, cause and duration of ESRD, and previous transplantation. Findings were very similar in models that censored at transplantation, ignored transplantation, or used transplantation as a time-dependent covariate; only findings using the last approach are presented here. Analyses were repeated after excluding 3564 patients without Medicare as primary payer or with ESRD of <90 d duration as of December 31, 1993. Excluding these patients did not alter the findings meaningfully; therefore, only the analysis of the larger sample is presented. All analyses were performed using SAS/STAT, version 8.2 (SAS Institute, Inc., Cary, NC).

Results

A total of 14,829 patients were studied. Table 1 shows the baseline characteristics of the study population on December 31, 1993. The mean patient age and duration of ESRD were 60.0 and 3.2 yr, respectively. Of all patients, 51.9% were male, 50.9% were white, 40.7% had diabetes, and 20.0% had ESRD for at least 5 yr. Table 1 also shows that albumin-adjusted calcium quintiles were ≤8.7, 8.8 to 9.2, 9.3 to 9.6, 9.7 to 10.2, and >10.2 mg/dl. The corresponding values for phosphorus were ≤4.4, 4.5 to 5.3, 5.4 to 6.3, 6.4 to 7.5, and >7.5 mg/dl; for calcium-phosphorus product were ≤40.9, 41.0 to 50.1, 50.2 to 59.2, 59.3 to 71.0, and >71.0 mg^2/dl^2; and for PTH were ≤37, 38 to 99, 100 to 210, 211 to 480 and >480 pg/ml.

The mean follow-up duration was 3.9 yr. During the follow-up period, 4.9% were hospitalized with a myocardial infarction, 31.4% with congestive heart failure, 7.1% with a stroke or transient ischemic attack, 9.6% with peripheral vascular disease, and 65.0% with one of these events; 77.2% had nonfatal or fatal cardiovascular events, and 79.1% died from any cause. Table 2 shows adjusted hazards ratios (AHR) for nonfatal or fatal cardiovascular events, the primary study outcome, as well as for all-cause mortality. Calcium levels in the fifth quintile were associated with an AHR of 1.08 for cardiovascular events; calcium levels in the second, fourth, and fifth quintiles were associated with mortality AHR of 1.07, 1.11, and 1.14, respectively. Phosphorus levels were associated with a monotonic risk for cardiovascular events: Second quintile, AHR 1.06; third, AHR 1.13; fourth, AHR 1.14; and fifth, AHR 1.25. Phosphorus levels were associated with all-cause mortality in the fourth (AHR 1.10) and fifth (AHR 1.19) quintiles. Calcium-phosphorus product levels in the third (AHR 1.09), fourth (AHR 1.14), and fifth (AHR 1.24) quintiles were associated with cardiovascular events, and levels in the fourth (AHR 1.09) and fifth (AHR 1.19) quintiles were associated with all-cause mortality. PTH levels in the fifth quintile were associated with both cardiovascular events (AHR 1.12) and all-cause mortality (AHR 1.17).

Figures 1 and 2 show AHR for cardiovascular events and death for the eight possible combinations that resulted when calcium, phosphorus, and PTH were dichotomized using the values 5.5 mg/dl, 10.2 mg/dl, and 408 pg/ml (the population mean), respectively. Compared with the reference category of phosphorus ≤5.5 mg/dl, calcium ≤10.2 mg/dl, and PTH ≤408 pg/ml, the largest AHR (1.35 for cardiovascular events and 1.30 for death) were seen in the combination of phosphorus >5.5 mg/dl, calcium >10.2 mg/dl, and PTH >408 pg/ml.

Discussion

We found that disorders of bone mineral metabolism, especially high phosphorus and calcium-phosphorus product levels, were associated with higher rates of cardiovascular events and death in hemodialysis patients. Our findings support the work of other researchers, who examined mortality rates using data sets that partially overlapped with those chosen for this study. For example, Block *et al.* (11) analyzed the distribution of serum phosphorus in two United States Renal Data System studies, the Case Mix Adequacy Study (1990) and the Dialysis Morbidity and Mortality Study Wave 1 Study (1993). They

Table 1. Baseline characteristics of the study population (n = 14,829)

Characteristic	% of Study Population
Age (yr)	
<45	19.2
45 to 64	36.5
≥65	44.3
Gender	
male	51.9
female	48.1
Race	
white	50.9
black	39.0
other	10.1
Former or current smoker	32.3
Cause of ESRD	
diabetes	32.5
hypertension	30.0
glomerulonephritis	13.7
other	23.8
Duration of ESRD (yr)	
<1.0	30.5
1.0 to 4.9	49.5
5.0 to 9.9	13.7
≥10.0	6.3
Previous renal transplantation	7.1
Body mass index (kg/m^2)	
<18.5	5.8
18.5 to 24.9	43.7
25.0 to 29.9	23.9
≥30.0	16.7
missing	9.9
Kt/V	
<1.0	18.7
1.0 to 1.1	23.1
1.2 to 1.3	19.2
≥1.4	15.1
missing	23.9
Albumin (g/dl)	
≤3.4	20.1
3.5 to 3.7	21.9
3.8 to 3.9	18.4
4.0 to 4.1	14.4
>4.1	14.7
missing	10.5
Hemoglobin (g/dl)	
≤8.8	19.3
8.9 to 9.7	19.3
9.8 to 10.4	18.0
10.5 to 11.2	17.5
>11.2	17.5
missing	8.4
Calcium (mg/dl)	
≤8.7	18.5
8.8 to 9.2	18.1
9.3 to 9.6	18.1
9.7 to 10.2	18.1
>10.2	17.8
missing	9.4
Phosphorus (mg/dl)	
≤4.4	19.7
4.5 to 5.3	17.2
5.4 to 6.3	18.7
6.4 to 7.5	16.9
>7.5	18.0
missing	9.5
Calcium × phosphorus product (mg^2/dl^2)	
≤40.9	18.0
41.0–50.1	18.0
50.2–59.2	18.0
59.3–71.0	18.0
> 71.0	18.0
missing	10.0
Parathyroid hormone (pg/dl)	
≤37	13.1
38 to 99	12.7
100 to 210	12.7
211 to 480	12.8
>480	12.8
missing	35.9
Comorbid conditions	
diabetes mellitus	40.7
coronary artery disease[a]	36.7
congestive heart failure	39.7
stroke or transient ischemic attack	16.3
peripheral vascular disease	24.5
malignancy	9.4
chronic lung disease	12.5

[a]History of coronary artery disease included one of the following: Angina, coronary artery disease, abnormal angiogram, angioplasty, coronary artery bypass grafting, and myocardial infarction.

found that adjusted mortality risks increased with serum phosphorus levels >6.5 mg/dl. As in our study, mortality associations were similar for serum phosphorus and calcium-phosphorus product, with mortality rates 34% higher in those with products in the fifth quintile (calcium-phosphorus product, >72 mg^2/dl^2). Log-transformed PTH levels also were associated with higher mortality rates (11). Ganesh *et al.* (12) examined overall mortality and cause-specific mortality using the Waves 1, 3, and 4 Study, as we did, and the earlier Case Mix Adequacy Study. They found higher mortality rates attributed

Table 2. Hazards ratios[a] (and 95% confidence intervals) for cardiovascular events and death

	Cardiovascular Event[b] (11,272/14,598[c]; 77.2%)	Death (11,730/14,829; 79.1%)
Calcium quintiles (mg/dl)		
≤8.7	1.00	1.00
8.8 to 9.2	1.03 (0.97 to 1.09)	1.07 (1.01 to 1.14)[d]
9.3 to 9.6	1.04 (0.97 to 1.10)	1.05 (0.99 to 1.12)
9.7 to 10.2	1.03 (0.97 to 1.10)	1.11 (1.04 to 1.18)[d]
>10.2	1.08 (1.01 to 1.15)[d]	1.14 (1.07 to 1.21)[e]
missing	1.17 (0.93 to 1.47)	1.03 (0.83 to 1.29)
Phosphorus quintiles (mg/dl)		
≤4.4	1.00	1.00
4.5 to 5.3	1.06 (1.00 to 1.13)[d]	1.02 (0.96 to 1.09)
5.4 to 6.3	1.13 (1.06 to 1.19)[e]	1.02 (0.96 to 1.08)
6.4 to 7.5	1.14 (1.07 to 1.22)[e]	1.10 (1.04 to 1.17)[d]
>7.5	1.25 (1.17 to 1.33)[e]	1.19 (1.12 to 1.27)[e]
missing	1.13 (0.90 to 1.41)	1.19 (0.96 to 1.47)
Calcium × phosphorus product (mg^2/dl^2)		
≤40.9	1.00	1.00
41.0 to 50.1	1.04 (0.98 to 1.11)	0.99 (0.94 to 1.06)
50.2 to 59.2	1.09 (1.03 to 1.16)[d]	1.05 (0.99 to 1.12)
59.3 to 71.0	1.14 (1.07 to 1.22)[e]	1.09 (1.03 to 1.16)[d]
>71.0	1.24 (1.16 to 1.32)[e]	1.19 (1.12 to 1.27)[e]
missing	1.23 (1.08 to 1.39)[d]	1.12 (0.99 to 1.26)
Parathyroid hormone (pg/dl)		
≤37	1.00	1.00
38 to 99	1.03 (0.96 to 1.11)	1.06 (0.99 to 1.14)
100 to 210	1.04 (0.97 to 1.12)	1.07 (0.99 to 1.15)
211 to 480	1.04 (0.96 to 1.13)	1.07 (0.99 to 1.15)
>480	1.12 (1.04 to 1.21)[d]	1.17 (1.08 to 1.26)[e]
missing	1.06 (0.99 to 1.13)	1.12 (1.06 to 1.19)[e]

[a]Using Cox regression with all of the characteristics shown in the first column of Table 1 entered simultaneously, with the exception of calcium-phosphorus product. Hazards ratios for calcium-phosphorus product were adjusted for all variables except calcium and phosphorus.

[b]Hospitalization for ischemic heart disease, congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease, or cause of death on the ESRD Death Notification Form attributed to cardiac causes, cerebrovascular accident, or ischemic brain damage.

[c]Denominator <14,829 reflects negative follow-up intervals.

[d]$P < 0.05$.

[e]$P < 0.0001$.

to coronary artery disease, sudden death, infection, and unknown causes with phosphorus levels >6.5 mg/dl. In addition, sudden death was associated with higher calcium-phosphorus product levels and PTH levels >495 pg/ml (12). Although we found similar mortality associations in this study, associations between phosphorus levels and cardiovascular events were apparent at phosphorus levels <5.5 mg/dl.

In a recently published study of 40,538 hemodialysis patients, Block *et al.* (16) also examined the associations among disorders of mineral metabolism, mortality, and cardiovascular hospitalizations. They found that after adjustment for demographic and laboratory covariates, serum phosphorus concentrations >5.0 mg/dl were associated with an increased relative risk of death (1.07, 1.25, 1.43, 1.67, and 2.02 for serum phosphorus 5.0 to 6.0, 6.0 to 7.0, 7.0 to 8.0, 8.0 to 9.0, and ≥9.0 mg/dl, respectively) and cardiovascular hospitalizations (1.10, 1.15, 1.29, 1.28, and 1.38 for serum phosphorus 5.0 to 6.0, 6.0 to 7.0, 7.0 to 8.0, 8.0 to 9.0, and ≥9.0 mg/dl, respectively). Albumin-adjusted serum calcium concentrations >9.5 mg/dl also were significantly associated with mortality but not cardiovascular hospitalizations. PTH levels ≥600 pg/ml also were associated with a significantly increased risk for death (relative risk [95% confidence interval], 1.08 [0.97 to 1.20], 1.18 [1.03 to 1.35], and 1.24 [1.09 to 1.41] for PTH 600 to 900, 900 to 1200, and ≥1200 pg/ml, respectively) and cardiovascular hospitalizations (1.17 [1.06 to 1.29]). Although our findings were broadly similar, the magnitude of the hazards ratios seen in our study (for calcium-related variables) was somewhat lower. We are uncertain as to the reason for the lower risk estimates in our study. It is possible that the disparities can be partially explained by some of the following:

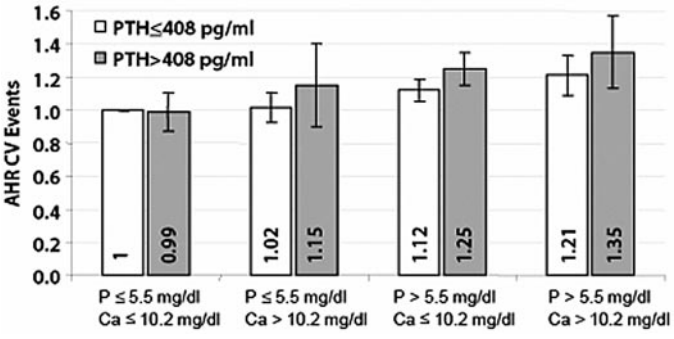

Figure 1. Cardiovascular (CV) events. Adjusted hazards ratios (AHR) for combinations of low and high levels of calcium, phosphorus, and parathyroid hormone (PTH). Adjustment has been made for the characteristics shown in Table 1. Reference category: Patients with phosphorus ≤5.5 mg/dl, calcium ≤10.2 mg/dl, and PTH ≤408 pg/ml. Error bars represent 95% confidence intervals.

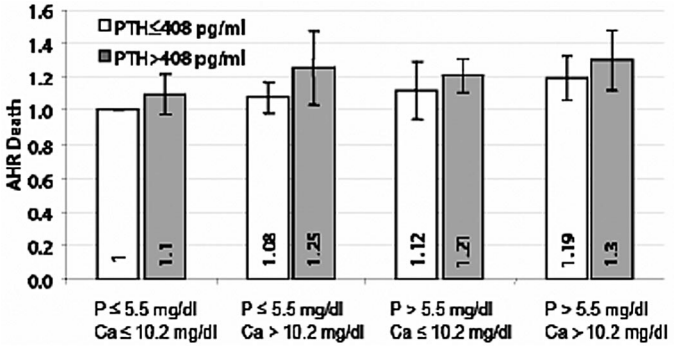

Figure 2. Death. AHR for combinations of low and high levels of calcium, phosphorus, and PTH. Adjustment has been made for the characteristics shown in Table 1. Reference category: Patients with phosphorus ≤5.5 mg/dl, calcium ≤10.2 mg/dl, and PTH ≤408 pg/ml. Error bars represent 95% confidence intervals.

Choice of reference groups, adjustment covariates, categorization of calcium-related variables, and follow-up intervals.

Other researchers found an inverse relationship of PTH level on enrollment to renal replacement therapy and mortality (17). It is possible that PTH level carries different significance in incident as opposed to prevalent hemodialysis patients; prospective studies with both incident and repeated measurements of PTH level are needed to answer this question.

High levels of PTH have been implicated in decreased cardiac contractility, myocardial hypertrophy and fibrosis, myocardial calcium deposition, vascular calcification, and impaired insulin secretion (18,19). In patients who are on hemodialysis, higher levels of PTH have been associated with mitral annulus calcification, which in turn seems to be associated with cardiac arrhythmias (20). Animal models of uremia suggest that PTH may play a permissive role in interstitial myocardial fibrosis (21), BP-independent wall thickening of intramyocardial arterioles (22), and impaired endothelial vasodilatory function (23), all of which might directly contribute to morbidity and mortality from cardiac causes secondary to arrhythmias, ischemia, and decreased left ventricular function. The mechanism by which high calcium-phosphorus product could lead to vascular calcification, arterial stiffening (24), and cardiovascular disease remains to be elucidated.

Our study differs in a number of respects from previous studies. We used cardiovascular hospitalizations as well as all-cause and cause-specific mortality as outcomes. Nonfatal and fatal cardiovascular events were studied, as opposed to purely cause-specific mortality, because the latter has been found to be relatively inaccurate in other studies (25). Several studies have found high specificity but low sensitivity for claims data for many diagnoses, including ischemic heart disease and stroke (26,27), so true event rates are likely to be underestimated. If one hypothesizes that abnormalities of calcium-phosphorus homeostasis cause death via cardiovascular mechanisms alone, all-cause mortality may also underestimate event rates. These were the considerations underlying our use of both nonfatal and fatal cardiovascular events.

Our study has several limitations. It is a retrospective observational study, and causal relationships cannot be inferred. It involves a prevalent cohort of hemodialysis patients; therefore, the patients included were not studied at a uniform phase of their chronic kidney disease. Calcium, phosphorus, and PTH were studied at one time point, so time-integrated risk exposures were unknown. Assays for biochemical parameters were not standardized. Pertinent medication data were not readily available, and biochemical data sets were incomplete. Medicare admissions were used to define cardiovascular events. Finally, it may or may not be possible to generalize findings from a cohort of patients who were studied more than one decade ago to current dialysis populations.

Despite these limitations, our findings may have clinical implications. The therapeutic armamentarium has widened considerably in the past decade to include calcium-free and aluminum-free phosphorus-binding drugs, new vitamin D analogues, calcimimetic drugs, and individualized dialysate calcium concentrations (28). Prevention of bone disease is clearly important. Prevention of cardiovascular disease may be as important. Our study suggests that phosphorus, calcium-phosphorus product, and PTH levels should be managed as treatable cardiovascular risk factors in dialysis patients. It is a universal truth that observational studies cannot fully account for residual confounding. Randomized, controlled trials are needed to determine whether the associations seen in this study reflect causal relationships or residual confounding.

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