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Association of Elevated Serum PO_4, Ca × PO_4 Product, and Parathyroid Hormone with Cardiac Mortality Risk in Chronic Hemodialysis Patients

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Abstract. Hyperphosphatemia is highly prevalent among patients with end-stage renal disease (ESRD) and is associated with increased mortality risk in hemodialysis (HD) patients. The mechanism through which this mortality risk is mediated is unclear. Data from two national random samples of HD patients (n = 12,833) was used to test the hypothesis that elevated serum PO_4 contributes mainly to cardiac causes of death. During a 2-yr follow-up, the cause-specific relative risk (RR) of death for patients was analyzed separately for several categories of cause of death, including coronary artery disease (CAD), sudden death, and other cardiac causes, cerebrovascular and infection. Cox regression models were fit for each of the eight cause of death categories, adjusting for patient demographics and non-cardiovascular comorbid conditions. Time at risk for each cause-specific model was censored at death that resulted from any of the other causes. Higher mortality risk was seen for patients in the high PO_4 group (>6.5mg/dl) compared with the lower PO_4 group (≤6.5mg/dl) for death resulting from CAD (RR 1.41; $P < 0.0005$), sudden death (RR 1.20; $P < 0.01$), infection (RR 1.20; $P < 0.05$), and unknown causes (RR 1.25; $P < 0.05$). Patients in the high PO_4 group also had non-significantly increased RR of death from other cardiac and cerebrovascular causes of death. The RR of sudden death was also strongly associated with elevated Ca × PO_4 product (RR 1.07 per 10 mg^2/dl^2; $P < 0.005$) and serum parathyroid hormone levels greater than 495 pg/ml (RR 1.25; $P < 0.05$). This study identifies strong relationships between elevated serum PO_4, Ca × PO_4 product, and parathyroid hormone and cardiac causes of death in HD patients, especially deaths resulting from CAD and sudden death. More vigorous measures to reduce the prevalence of these factors in HD patients may result in improved survival.

Hyperphosphatemia is a common problem among patients with ESRD. It is a highly prevalent condition, as almost 40% of the U.S. hemodialysis population has a serum PO_4 greater than 6.5 mg/dl (1). Elevated serum PO_4 has been associated with the progression of secondary hyperparathyroidism, deposition of calcium in soft tissues, and the development of cutaneous calciphylaxis. Recently, Block *et al.* from the United States Renal Data System (USRDS) identified in multivariate analysis elevated serum PO_4 as an independent predictor of mortality (1). The overall mortality risk associated with serum PO_4 above 6.5 mg/dl was 27% greater than that of patients with PO_4 levels between 2.4 and 6.5 mg/dl. In the same study, elevated Ca × PO_4 product greater than 72 mg^2/dl^2 was also associated with increased mortality risk (RR 1.34; $P < 0.01$).

The finding of increased mortality in this study raised several questions as to the potential mechanisms through which elevated PO_4 may contribute to increased mortality risk in ESRD patients. It is speculated that elevated PO_4 may aggravate the effects of coronary atherosclerosis through increased vascular calcification and smooth muscle proliferation (2). It has also been suggested that myocardial calcification, a consequence of elevated PO_4, may alter microcirculatory hemodynamics through increased extravascular resistance and further compromise myocardial perfusion (3). We, therefore, hypothesized that the increased mortality risk associated with elevated PO_4 levels was primarily related to cardiac rather than non-cardiac causes of death.

To explore this hypothesis, we undertook a national study of prevalent HD patients to determine the association of serum PO_4 with cause-specific mortality. Specifically, the purpose of this study was to (*1*) identify the causes of death that were significantly related to increased serum PO_4; (*2*) determine the relative magnitude of association with each of eight causes of death; (*3*) determine the association of elevated Ca × PO_4 product with cause-specific mortality; and (*4*) determine the association of parathyroid hormone (PTH) with cause-specific mortality. The availability of data from two large USRDS national studies, the Case Mix Adequacy Study (CMAS) and the Dialysis Morbidity and Mortality Study (DMMS) waves 1, 3, and 4 allowed us a unique opportunity to further explore these relationships.

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Materials and Methods

Data

Data used in this analysis were obtained from two special studies of the USRDS: the CMAS and the DMMS waves 1, 3 and 4. The CMAS was a national random sample of HD patients who were alive on December 31, 1990. The sample included 7096 prevalent HD patients who were randomly selected from 523 HD facilities. A systematic sampling technique identified the primary sampling units (dialysis facilities), and patients were randomly selected from these on the basis of the last two digits of their social security number. For patients who developed ESRD before January 1, 1990, data were collected as of the study start date, which was December 31, 1990, and for those who developed ESRD during 1990, data were collected as of 1 mo after their first dialysis treatment. Survival analyses for all patients started on January 1, 1991. Dialysis facility personnel abstracted baseline data on all patients from the medical records. Data collected included; patient identifiers, health insurance information, the presence or absence of a number of comorbid medical conditions occurring within 10 yr before study start date, and laboratory data just before study start.

The DMMS waves 1, 3, and 4 were historical prospective studies in which data were collected on a random sample of 15,598 prevalent patients who were alive on December 31, 1993, from over 1300 dialysis units throughout the United States. These dialysis units again were randomly chosen from the master list of Medicare-approved dialysis facilities. From these sampling units, one in five patients was selected to give the desired sample size. During 1995, dialysis unit personnel abstracted patient data from medical records, using forms created by the USRDS Coordinating Center and tested by the USRDS Networks. The study start date for patients in the DMMS waves 1, 3, and 4 was December 31, 1993. The period of follow-up for patients in both studies was 2 yr from the start of the study.

Analytical Methods

To obtain follow-up data on all members of the cohort, the CMAS and the DMMS waves 1, 3, and 4 datasets were linked to the USRDS database, which contains longitudinal data on all Medicare ESRD patients from 1977 to the present. The primary dataset was supplemented with data on race, primary cause of ESRD, date of first dialysis service, date of any kidney transplant, date of death, and causes of death. Causes of death were obtained from the Health Care Financing Administration (HCFA) ESRD Death Notification Form (HCFA-2746-U3), which lists 59 categories for cause of death. The HCFA ESRD Death Notification Form serves as the primary source of information on cause of death for ESRD patients in the United States. The USRDS files include a "missing cause of death" category for patients for whom no Death Notification Form was received. For the purposes of this study, the 59 causes of death on the HCFA Death Notification Form were collapsed into 8 causes of death categories as summarized in Table 1: coronary artery disease, other cardiac, cerebrovascular, infection, sudden death, other, unknown, and missing.

The main analyses were limited to prevalent patients receiving thrice-weekly HD treatments, excluding about 5% of patients, who received twice weekly HD. Patients were systematically excluded from the original dataset if the Medicare identification number prevented linking with existing USRDS datafiles, if bicarbonate was not used in the dialysate (<5% of patients), if data were missing for more than half of the comorbid conditions, serum calcium, PO_4, serum albumin, or age at study start, or if the number of days at risk could not be calculated. Following exclusion ($N_{CMAS} = 2892$ and $N_{DMMS} = 6503$), a

Table 1. Categorization of causes of death on Death Notification Form (HCFA-2746)

Category	Cause of Death
Coronary artery disease	Acute myocardial infarction
	Atherosclerotic heart disease
Other cardiac	Valvular heart disease
	Cardiomyopathy
	Cardiac arrhythmia
	Pericarditis, including cardiac tamponade
	Pulmonary edema resulting from exogenous fluid
Sudden death	Cardiac arrest
	Hyperkalemia
Cerebrovascular	Cerebrovascular accident, including cerebral hemorrhage
	Ischemic brain damage/anoxic encephalopathy
Infection	Septicemia, vascular access
	Septicemia, peritonitis
	Septicemia, peripheral vascular disease/gangrene
	Septicemia, other
	Pulmonary infection, bacterial
	Pulmonary infection, fungal
	Pulmonary infection, other
	Viral infection, cytomegalovirus
	Viral infection, other
	Tuberculosis
	AIDS
	Infection, other
	Hepatitis B
	Other viral hepatitis
	Fungal peritonitis
Other	Malignant disease, immunosuppressive
	Malignant disease
	Pulmonary embolus
	Liver-drug toxicity
	Cirrhosis
	Polycystic liver disease
	Liver failure—cause unknown
	Gastrointestinal hemorrhage
	Hemorrhage from transplant site
	Hemorrhage from vascular access
	Hemorrhage from dialysis circuit
	Hemorrhage from ruptured vascular aneurysm
	Hemorrhage from surgery
	Other hemorrhage
	Mesenteric infarction
	Pancreatitis
	Perforation of peptic ulcer
	Perforation of bowel
	Bone marrow suppression
	Dementia
	Seizures
	Diabetic coma
	Chronic obstructive lung disease
	Complications of surgery
	Ischemic brain/anoxic encephalopathy
	Air embolism
	Accident related to treatment
	Accident unrelated to treatment
	Suicide
	Drug overdose, street drugs
	Drug overdose, not suicide or street drugs
	Cachexia
	Other identified cause
Unknown	Cause of death unknown
Missing	Cause of death missing

total of 12,833 patients from the combined datasets were included for these analyses.

The independent variables of interest were the predialysis level of serum PO_4, Ca × PO_4 product, and PTH. As data on PO_4 binder therapy was available for only a small subset of patients included in waves 3 and 4 of the DMMS study, its association with cause-specific mortality was not addressed. Of the variables listed, serum PO_4 was first entered alone as a continuous variable to determine the presence of a linear relationship with cause-specific mortality. Similar models were constructed to determine the relationship of Ca × PO_4 product and PTH with each specific cause of death. A second model explored the relationship of high serum PO_4 (>6.5 mg/dl) to each specific cause of death category compared with the reference group (PO_4, 2.4 to 6.5 mg/dl). The dependent variable was the time to cause-specific death.

Cox proportional hazard regression techniques were used to explore the relationship of elevated serum PO_4 with death in each cause-specific death category. Patients were followed until the earliest of the following: death, loss to follow-up, transplantation, or 2 yr from study start date. For each cause-specific model, the time at risk was censored at death resulting from any other of the causes listed (*i.e.*, patients are at risk for a specific cause of death until they die from another cause). A total of 24 Cox proportional regression models were fit to calculate the relative risk of mortality for each of the eight causes of death and the following baseline laboratory values: serum PO_4, Ca × PO_4 product, and serum PTH. The main analyses were adjusted for patient age at study start, duration of ESRD, gender, race, cause of ESRD, and non-cardiovascular comorbid conditions.

Several sensitivity analyses were performed by using Cox regression modeling to determine whether or not the relationships between serum PO_4 and cardiac causes of death were still apparent when adjustment was made for additional known mortality predictors (4, 5, 6,7,8) at study start. For these analyses, adjustment was made for the presence of atherosclerotic conditions (coronary artery and cerebrovascular and peripheral vascular occlusive disease), indicators of nutrition, anemia, a measure of noncompliance (skipping one or more dialysis treatments per month), as well as delivered dose of dialysis. The delivered dose of dialysis was estimated using the Daugirdas formula (9):

$$\text{Delivered Kt/V} = -\ln(R - 0.008*t) + (4 - 3.5R)*UF/W$$

where R = postdialysis/predialysis blood urea nitrogen, t = hr of dialysis, UF = predialysis-postdialysis weight change, and W = postdialysis weight. An average of at least three Kt/V readings per patient (maximum six) recorded over a 6-mo period before the study start date were used in these analyses.

We tested for the presence of several interactions that might modify the relationship between serum PO_4 and cause-specific mortality. We specifically explored the relationship of dialysis duration with PO_4, Ca × PO_4 product, and PTH and cardiac causes of death, as we hypothesized that the duration of exposure of these factors might increase the magnitude of mortality risk. Tests of proportionality were performed to ensure that the proportional hazards assumption was not violated in these analyses. All analyses were carried out using SAS statistical software (V6.12, SAS Institute, Cary NC).

Results

Data on serum PO_4 were available for 12,833 patients from the combined data sets. Data on Ca × PO_4 was available for 9095 patients and on serum PTH for 6634 patients from the DMMS only. The distribution of demographics, comorbidities, and laboratory variables for the entire study population is given in Table 2. The mean serum PO_4 level was 6.2 ± 2.0 mg/dl. The mean Ca × PO_4 product and serum PTH was 57 ± 19 mg^2/dl^2 and 387 ± 783 ng/ml, respectively.

There were 4120 deaths among the 12,833 patients during the 2-yr period of follow-up. The distribution of causes of death for all members of the study cohort is given in Table 3. Deaths resulting from sudden death accounted for the greatest

Table 2. Characteristics of study population from the combined Dialysis Morbidity and Mortality Study waves 1, 3, and 4 and Case Mix Adequacy Study data sets (n = 12,833)

Patient Characteristics	Mean ± SD or %
Demographics	
age of onset of ESRD (yr)	53.8 ± 16.6
age at study start date (yr)	58.2 ± 15.6
race (% black)	42.0
gender (% male)	50.3
cause of ESRD (% diabetes)	30.4
mean duration of ESRD at study start date (yr)	4.4 ± 3.7
Laboratory values	
serum albumin (g/dl)	3.8 ± 0.4
serum phosphorous (mg/dl)	6.2 ± 2.0
serum calcium (mg/dl)	9.4 ± 1.0
Ca × PO_4 (mg^2/dl^2)	57 ± 19
serum i-PTH (pg/ml)	387 ± 783
hematocrit (%)	30.3 ± 4.6
serum creatinine (mg/dl)	11.4 ± 3.6
Dialysis dose and compliance	
delivered dose (Kt/V)	1.2 ± 0.1
skipped ≥1 dialysis session per mo (%)	8.5
Comorbid conditions (% yes or suspected)	
diabetes (history and/or nephropathy)	39.3
coronary artery disease[a]	43.5
congestive heart failure	42.0
left ventricular hypertrophy	34.6
cerebrovascular disease (history of stroke or TIA)	13.4
peripheral vascular disease[b]	26.7
chronic obstructive lung disease	12.3
smoking (active)	22.7
AIDS	0.5
neoplasm (history)[c]	9.4
body mass index (kg/m^2)	24.8 ± 5.7

[a] Includes history of coronary artery disease, coronary artery bypass surgery, angioplasty, or abnormal angiography.
[b] Includes history of peripheral vascular disease, amputation, absent pulses, and claudication.
[c] Excludes basal and squamous cell carcinoma of the skin.
ESRD, end-stage renal disease.

percentage of all deaths (27%), and deaths resulting from cerebrovascular disease accounted for the smallest percentage of all deaths (4.6%). Deaths resulting from CAD and other cardiac causes (excluding sudden deaths) accounted for almost 20% of all deaths in this cohort. In 5.9% of patients, the cause of death was not available for categorization.

The adjusted relative risk (RR) of death by cause of death for serum PO_4 as a continuous variable (per 1 mg/dl) is illustrated in Figure 1. Each bar represents a separate Cox analysis. A 1 mg/dl increment in serum PO_4 was associated with an 9% higher risk of death resulting from CAD ($P < 0.0005$) and a 6% higher risk of death resulting from sudden death ($P < 0.01$), when adjusting for age at study start, duration of ESRD, race, gender, diabetes, smoking, AIDS, and neoplasm. The relationships of increased serum PO_4 with deaths resulting from CAD and sudden deaths were particularly strong and statistically significant. Elevated serum PO_4 was also significantly associated with deaths resulting from cerebrovascular disease (RR 1.08; $P < 0.05$), infection (RR 1.05; $P < 0.05$), and unknown causes of death (RR 1.07; $P < 0.05$).

The relationship between serum PO_4 and cause-specific mortality was further explored with serum PO_4 as a categorical variable. This was done, as our group has previously shown that the relationship between serum PO_4 and all-cause mortality is nonlinear with increased mortality risk seen only with serum PO_4 levels >6.5 mg/dl (1). For these analyses, the adjusted RR of death by cause of death for serum PO_4 >6.5 mg/dl compared with serum PO_4 level between 2.4 to 6.5 mg/dl was explored and is illustrated in Figure 2. Again, higher mortality risks were observed for patients in the high PO_4 group compared with the reference group in the categories of deaths resulting from CAD and sudden death as well as deaths resulting from infection and unknown causes of death.

Patients with serum PO_4 >6.5 mg/dl had the greatest excess risk for CAD deaths (RR 1.41; $P < 0.0005$). This hazard ratio was twice as high as that for all causes combined (RR 1.21; $P < 0.0005$). Further Cox regression models were constructed to compare the risk of death from CAD with that from all non-CAD causes combined for patients with substantial hyperphosphatemia. The risk estimates are illustrated in Figure 3. The RR of death resulting from CAD was substantially greater than that from a non-CAD cause of death on comparing the high PO_4 group with the reference group. A comparison of risk ratios confirmed that the risk of CAD deaths was significantly greater than the risk of non-CAD deaths ($P < 0.05$) in prevalent HD patients with elevated PO_4 levels.

Table 3. Distribution of causes of death in study population

Cause of Death	*n* (%)
Coronary artery disease	525 (12.7)
Other cardiac	227 (5.5)
Cerebrovascular	190 (4.6)
Infection	523 (12.7)
Missing	242 (5.9)
Other	882 (21.4)
Sudden death	1,111 (27)
Unknown	420 (10.2)

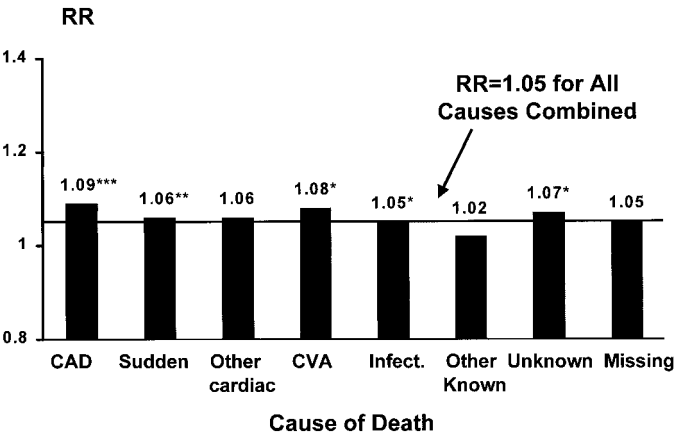

Figure 1. Adjusted relative risk (RR) of mortality by cause of death per 1 mg/dl higher serum PO_4 (eight Cox models). *$P < 0.05$; **$P < 0.001$; ***$P < 0.0005$ compared with RR of 1.0; CAD, coronary artery disease; CVA, cerebrovascular.

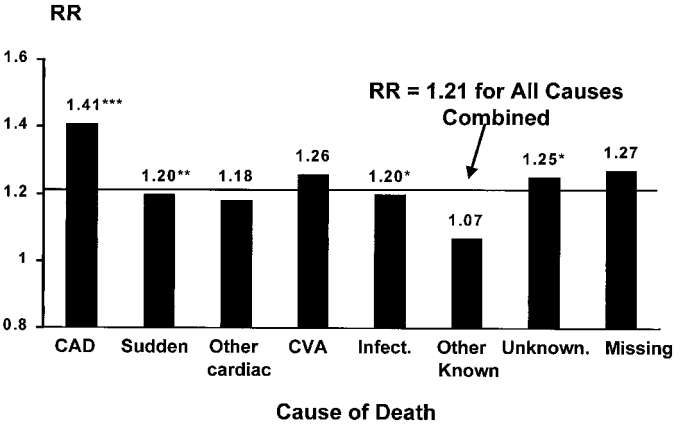

Figure 2. Adjusted RR of mortality by cause of death for serum PO_4 > 6.5 mg/dl *versus* 2.4 to 6.5 mg/dl (eight Cox models). *$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$ compared with RR of 1.0.

Several sensitivity analyses were performed to determine whether the relationship between elevated PO_4 and elevated CAD mortality risk could be explained by factors other than those included in the model. Known mortality predictors, including the presence of pre-existing medical conditions, anemia, indicators of nutrition, delivered dose of dialysis, and measures of non-compliance, were added to the main models and adjusted for in the analyses. These results are illustrated in Table 4. The relationship between elevated serum PO_4 and deaths resulting from CAD was not explained by skipped or missed dialysis treatments, inadequate dialysis delivery, degree of anemia, measures of nutrition, or the presence of pre-existing vasculopathy. Additional adjustment for pre-dialysis serum creatinine yielded an even stronger association between elevated serum PO_4 and CAD death risk (RR 1.53; $P < 0.0001$).

The association of elevated PO_4 with sudden death and

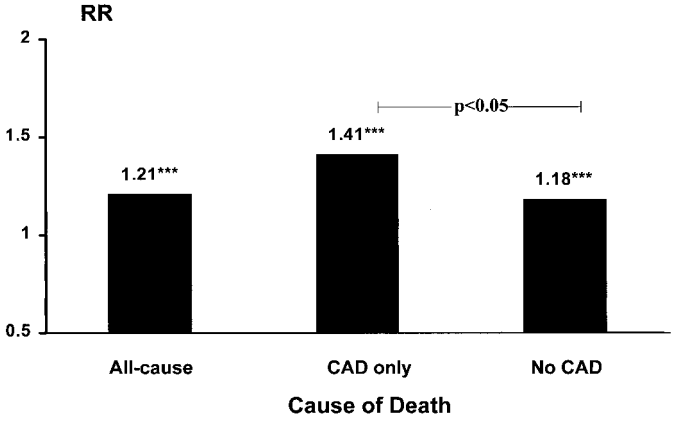

Figure 3. Adjusted RR of mortality for all causes and for CAD *versus* non-CAD causes (three Cox models) for $PO_4 > 6.5$mg/dl *versus* 2.4 to 6.5 mg/dL (reference). ***$P < 0.0005$ compared with RR of 1.0.

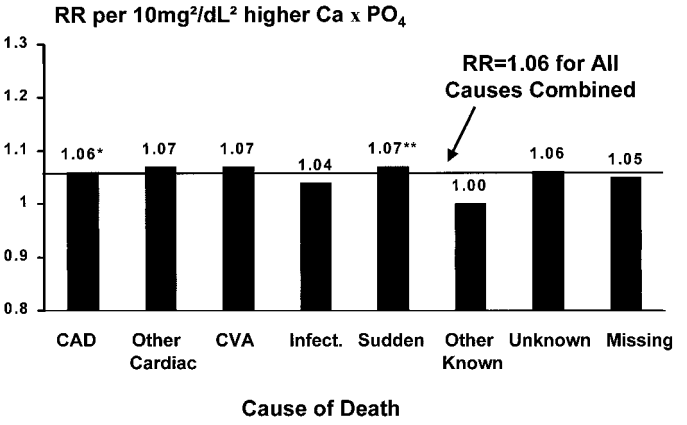

Figure 4. Adjusted RR of mortality by cause of death for Ca × PO_4 product per 10 mg^2/dl^2 higher (eight Cox models). *$P < 0.05$; **$P < 0.001$ compared with RR of 1.0.

Table 4. Relative risk of death resulting from coronary artery disease for patients with serum $PO_4 > 6.5$ mg/dl (*versus* 2.4 to 6.5 mg/dl): Sensitivity analyses ($n = 12{,}687$)

Covariate Adjustments	Relative Risk	*P*
Main model (age and duration of ESRD at study start, race, gender, diabetes, AIDS, neoplasm, active smoking)	1.41	< 0.0005
Main model + skipping ≥1 session/mo	1.41	< 0.0005
Main model + dose of dialysis (Kt/V)	1.41	< 0.0005
Main model + anemia (hematocrit)	1.42	< 0.0005
Main model + nutritional indices (BMI, creatinine, albumin)	1.39	< 0.005
Main model + atherosclerotic disease (coronary, cerebral, and peripheral)	1.51	< 0.0005
All of the above factors combined	1.36	< 0.01

infection as causes of death did not change following adjustment for these additional model covariates. The sensitivity analyses for elevated PO_4 and death risk resulting from other cardiac causes yielded some interesting observations. Although elevated serum PO_4 was not significantly related to deaths resulting from other cardiac causes in the main model (RR 1.18; $P = 0.25$), the final multivariate model, adjusted also for these additional variables, did yield a stronger and statistically significant association (RR 1.41; $P < 0.05$).

As elevated Ca × PO_4 product has also been shown to be associated with all-cause mortality among HD patients (1), we performed analyses to assess correlations with specific causes of death. As shown in Figure 4, among the listed cause of death categories, only deaths resulting from CAD (RR 1.06, $P < 0.05$) and sudden deaths were significantly related to elevated Ca × PO_4 product as a linear function (RR 1.07 per 10mg^2/dl^2; $P < 0.005$). When serum PO_4 was added to each model equation, the relationship between Ca × PO_4 product and these death categories were no longer apparent.

The impact of serum PTH on cause-specific mortality was explored for 6634 HD patients with available baseline PTH. A log transformation of serum PTH revealed a more normally distributed variable, and this was used in the statistical analyses. The log (PTH) was associated with cerebrovasular and sudden deaths as well as deaths from other cardiac and unknown causes. Of these, only the sudden death category was significantly related to log PTH in a nonlinear fashion. Figure 5 illustrates the U-shaped relationship of log (PTH) in quintiles with sudden death. Although an increased risk of sudden death was seen for patients with serum PTH values <33 pg/ml (RR 1.10) and >495 pg/ml (RR 1.06), compared with the reference group (PTH, 91 to 197 pg/ml), only the latter relationship reached statistical significance ($P < 0.05$).

We did not find evidence to support the hypothesis that the duration of ESRD modified the relationship between serum PO_4, Ca × PO_4 product, and PTH and cardiac causes of death. The *P*-values for these interactions were all >0.1.

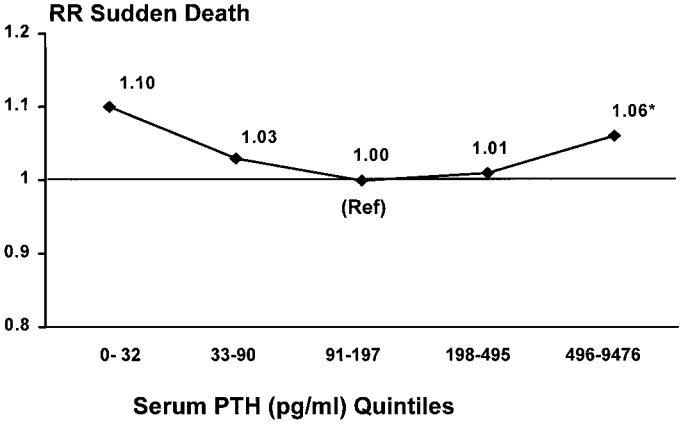

Figure 5. Adjusted RR of sudden death by serum PTH in quintiles. *$P < 0.05$ compared with RR of 1.0.

Discussion

This national study identifies specific causes of death that are associated with elevated serum PO_4, Ca × PO_4 product, and PTH in prevalent HD patients. We hypothesized that elevated serum PO_4 may independently contribute to cardiac causes of death through enhanced vascular calcification of atherosclerotic plaques and increased myocardial calcification. We found that patients with serum PO_4 >6.5 mg/dl have 41% greater risk of death resulting from CAD and a 20% greater risk of death resulting from sudden death compared with patients with serum PO_4 between 2.4 mg/dl and 6.5 mg/dl, adjusting for several known mortality predictors. We also found a 20% greater risk of death resulting from infection and unknown causes among patients with substantial hyperphosphatemia. These findings suggest that serum PO_4 at concentrations >6.5 mg/dl may be a major cardiotoxin for patients on chronic hemodialysis.

Elevated serum PO_4 was more strongly associated with deaths from CAD than any other cause of death category. This association was independent of several other factors known to affect mortality. Furthermore, a statistical comparison of death risks between CAD and non-CAD causes of death confirmed that elevated serum PO_4 preferentially predisposes to CAD deaths. This suggests a role for elevated serum PO_4 either in the development, progression, or the rupture of atheromatous plaques in the coronary arteries of prevalent ESRD patients.

There are several mechanisms through which elevated serum PO_4 may contribute to accelerated CAD. The development of vascular calcification, including plaque calcification, is a commonly cited mechanism for the accelerated atherosclerosis observed in ESRD patients. In experimental models of renal failure, the calcium content of the heart and the aorta is greatly increased (10). Further support for PO_4-mediated tissue calcification has come from the observations of Southwood *et al.* (11). In observational studies, they have identified elevated serum PO_4 as a strong risk factor for cardiac and vascular calcification. The recent observations of Goodman *et al.* also highlight the increased prevalence and extent of coronary artery calcification in young dialysis patients compared with normal controls (12). Higher serum PO_4, Ca × PO_4 product, and calcium intake was associated with increased coronary artery calcification. In addition to vascular calcification, elevated serum PO_4 may also contribute to vascular smooth muscle cell proliferation and compromise flow in the coronary microcirculation (13,14). As invasive imaging of the coronary arteries carries significant risk, ultrasonic measurement of carotid artery intima-media thickness has become a preferred method for monitoring the progression of arterial disease and has been shown to be a strong predictor of clinical coronary disease (15). Using high-resolution B-mode ultrasonography, Kawagashi *et al.* found that elevated serum PO_4 was strongly associated with changes in intima-media thickness of the carotid artery (16), an effect that was independent of several other commonly measured coronary risk factors.

This study also suggests that elevated serum PO_4 and Ca × PO_4 product may contribute to increased death rates from sudden death. We suspect that the "sudden death" label usually indicates unexpected deaths during the 2- to 3-d interdialytic interval and likely reflects deaths from undiagnosed myocardial infarction, cardiac arrhythmia, or cardiac arrest. This category accounted for the largest percentage of all deaths (27.5%) in the study population. For patients with a serum PO_4 >6.5 mg/dl *versus* 2.4 to 6.5 mg/dl, the RR of sudden death increased by 20%. Similarly, for every 10-unit higher Ca × PO_4 product, the RR of sudden death increased by 7% ($P < 0.005$). There are several mechanisms through which these aberrations in mineral metabolism could precipitate fatal cardiac events. These include myocardial calcification with disruption of the normal conduction system architecture and microvascular ischemia. In support of these mechanisms, Braun *et al.* found in a case-control study using electron beam computed tomography that the coronary artery calcium scores of dialysis patients were 2.5 to 5 times those of non-dialysis patients (17). More recently, Schwarz *et al.* have provided further evidence of increased coronary artery calcification among patients with ESRD, showing at autopsy that uremic patients had significantly more calcified coronary plaques than controls (2). These studies suggest that elevated Ca × PO_4 product may result in increased calcium deposition in coronary artery plaques and promote plaque rupture. There is also accumulating evidence for increased myocardial calcification in HD patients (18,19). Myocardial tissue calcification has been shown to correlate positively with elevated Ca × PO_4 product and inversely with left ventricular function (19). It is now recognized that myocardial calcification may also contribute to abnormalities in the coronary microcirculation through increased extravascular resistance and impairment of coronary blood flow (3).

An interesting finding from this study was the identification of an association between elevated serum PO_4 and unknown causes of death. The unknown cause of death category accounted for a nontrivial 10.2% of all patient deaths. The RR of death from an unknown cause was 25% higher for patients with serum PO_4 >6.5mg/dl compared with the reference group. Furthermore, the magnitude of this relationship increased after adjustment for several additional mortality predictors (RR 1.39; $P < 0.05$). Although it cannot be proven, it is tempting to suggest that many of these deaths may in fact be cardiac in origin. Sudden death events occurring in the interdialytic period may be recorded as unknown cause of death when in fact the underlying cause is cardiac arrhythmia or silent myocardial infarction.

Deaths resulting from other cardiac causes contributed to 5.7% of all patient deaths. This death category included deaths from valvular heart disease, cardiomyopathy, pericarditis, and pulmonary edema. Although the initial model (adjusting for age, race, gender, diabetes, smoking, AIDS, and neoplasm) did not support a statistically significant association, the final multivariate model with adjustment for several additional factors demonstrated a 41% increased risk of death from other cardiac causes among patients in the high PO_4 group. Calcification of the aortic and mitral valves, myocardium, and coronary arteries have been well described and are potential mechanisms

through which elevated serum PO_4 may contribute to these causes of death (17,20). The advent of electron beam computed tomography has permitted an evaluation of the prevalence and extent of calcification in the heart. Braun *et al.* found that the mitral valve was calcified in 59% of patients and that the aortic valve was calcified in 55% (17). Although this death category represents a very heterogeneous group, it is likely that some if not all of these are related to elevated serum PO_4.

The observations of Block *et al.* identified high serum PTH as a significant correlate of all-cause mortality (1). We speculated that elevations in serum PTH might be associated with increased risk of death from cardiac causes. Our analyses show that elevated PTH was significantly associated with sudden deaths among HD patients. The observed relationship had a U-shaped distribution; however, the increased death risk was significant only for patients with PTH values >495 pg/ml ($P < 0.05$). This effect was independent of changes in concentrations of serum PO_4 and Ca × PO_4 product also adjusted for in this analysis. The observation that patients with low PTH levels might also be at greater risk of sudden death was an unexpected finding. One could speculate that these might represent a subgroup of patients who have undergone parathyroidectomy for severe hyperparathyroidism. Accordingly, the lowest quintile group might contain a substantial number of patients who were at greatest risk of sudden death. The absence of available data on parathyroidectomy in our data set prevented us from further investigation of this relationship. This analysis provides further evidence on the role of parathyroid hormone as a potential cardiotoxin (21). Many published studies implicate parathyroid hormone as a permissive factor that promotes cardiac fibroblast activation and intermyocardiocytic fibrosis (22,23). Previous work in laboratory animals has shown regression in myocardial fibrosis following parathyroidectomy (23). It is likely that these changes in myocardial architecture may contribute to poor left ventricular compliance and diastolic dysfunction while also increasing the potential for fatal cardiac arrhythmias.

Patients with elevated serum PO_4 were also found to be at increased risk of death from infection (RR 1.37; $P < 0.03$). Of the entire study population, infection-related deaths accounted for 13.4% of all patient deaths. It is unclear how serum PO_4 may be related to infection-related deaths. Whether serum PO_4 directly or indirectly impairs immune system function has not to our knowledge been studied. It is conceivable that high serum PO_4 levels may be linked to infection related deaths through poor wound healing arising from abnormalities in the microcirculation.

The limitations of observational studies need to be considered when evaluating the importance of this study. First, we acknowledge the limitations associated with the use of prevalent cohorts of ESRD patients in assessing survival comparisons as individual patients may be at different time points in the course of their illness. To overcome this concern, we would suggest that this analysis be repeated in a cohort of incident ESRD patients to see if our findings can be reproduced. A second concern that has been raised previously relates to the current classification system for cause of death in ESRD patients. The primary responsibility for deciding on the cause of death lies with the patient's nephrologist. He or she may be aided in this duty by reviewing patients' medical records Although the cause of death might be obvious in some cases (*e.g.*, patient death occurring immediately after myocardial infarction without any other antecedent cause = *death from myocardial infarction*), in others it may be less clear. This categorization system does lend itself to error and the possibility of misclassification bias as the cause of death has not been standardized. However, study results would be compromised only if there was a selective difference in misclassification between the groups compared. Finally, although we adjusted for several well-known predictors of mortality, it is possible that other relevant factors were omitted from the model, which may completely or in part explain the effect of PO_4, Ca × PO_4 product, or PTH levels with cardiac mortality.

This study of prevalent HD patients describes the association of elevated PO_4 with several causes of death. It specifically highlights the strong association of elevated PO_4 with cardiac causes of death, especially those from CAD and sudden death. This study also suggests a role for serum PTH and elevated Ca × PO_4 product as important predictors of sudden deaths among prevalent HD patients. The identification of these factors as predictors of cardiac mortality has major implications. First, it suggests that there are mechanisms through which PO_4 may contribute to cardiac deaths of ESRD patients. The identification and elucidation of these mechanisms may be useful in reducing the burden of ESRD mortality. Second, as serum PO_4 and PTH concentrations are modifiable, measures should be targeted to reduce their levels in HD patients to improve survival.

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