Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis

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Abstract. Mortality rates in ESRD are unacceptably high. Disorders of mineral metabolism (hyperphosphatemia, hypercalcemia, and secondary hyperparathyroidism) are potentially modifiable. For determining associations among disorders of mineral metabolism, mortality, and morbidity in hemodialysis patients, data on 40,538 hemodialysis patients with at least one determination of serum phosphorus and calcium during the last 3 mo of 1997 were analyzed. Unadjusted, case mix–adjusted, and multivariable-adjusted relative risks of death were calculated for categories of serum phosphorus, calcium, calcium × phosphorus product, and intact parathyroid hormone (PTH) using proportional hazards regression. Also determined was whether disorders of mineral metabolism were associated with all-cause, cardiovascular, infection-related, fracture-related, and vascular access–related hospitalization. After adjustment for case mix and laboratory variables, 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). Higher adjusted serum calcium concentrations were also associated with an increased risk of death, even when examined within narrow ranges of serum phosphorus. Moderate to severe hyperparathyroidism (PTH concentrations ≥600 pg/ml) was associated with an increase in the relative risk of death, whereas more modest increases in PTH were not. When examined collectively, the population attributable risk percentage for disorders of mineral metabolism was 17.5%, owing largely to the high prevalence of hyperphosphatemia. Hyperphosphatemia and hyperparathyroidism were significantly associated with all-cause, cardiovascular, and fracture-related hospitalization. Disorders of mineral metabolism are independently associated with mortality and morbidity associated with cardiovascular disease and fracture in hemodialysis patients.

At present, >300,000 people in the United States are undergoing therapy for ESRD with the majority on in-center hemodialysis (1). Although extending the life of patients with ESRD should be considered one of the great medical accomplishments of the latter half of the 20th century, much remains to be improved. Mortality rates are in excess of 20% per year despite improved dialytic technology and the expenditure of considerable resources, >$22 billion per year as of 2001 (1).

Numerous studies have attempted to identify risk factors for mortality and morbidity in this population. Most have shown important relations among demographic factors (*e.g.*, older age, male gender, white race) and mortality (2,3). Comorbid conditions (*e.g.*, diabetes, cardiovascular disease) and laboratory proxies of nutritional status (*e.g.*, serum albumin, prealbumin, creatinine) have also been consistently associated with mortality and morbidity (4–6). Unfortunately, few of these factors are mutable. Of those factors that potentially are influenced by changes in dialysis practice, the intensity of dialysis, hemoglobin concentration, and control of mineral metabolism are among the most prominent. Much attention has been paid to dialysis dose, despite controversy regarding the validity of the most commonly used dose metric (*i.e.*, Kt/V_{urea}) (7,8) and mixed reports from observational data sources (9,10). Substantial benefits of high *versus* standard Kt/V_{urea} and high *versus* low flux membranes are unlikely based on the results of the HEMO study, a 2 × 2 factorial randomized clinical trial (11). Correction of anemia is achievable in the vast majority of patients with the use of recombinant erythropoietin and intravenous iron (12). Compared with dialysis dose and anemia, relatively little attention has been paid to disorders of mineral metabolism. Moreover, recently published quality targets in mineral metabolism have not been validated carefully (13). Herein we report the results of a comprehensive analysis of a large, nationally representative database of hemodialysis patients in which we aimed to identify evidenced-based targets for phosphorus, calcium, and parathyroid hormone (PTH), considering the relations among these variables with mortality and hospitalization, incorporating critically important confounding variables.

Materials and Methods

Data Source

The sample of patients was taken from the Fresenius Medical Care North America Patient Statistical Profile system. The database and

Received March 9, 2004. Accepted April 27, 2004.

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1046-6673/1508-2208
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000133041.27682.A2

methods of abstraction have been previously described (14). The cohort consisted of patients who were on thrice-weekly hemodialysis as of January 1, 1998, and had at least one determination of serum phosphorus and calcium during the last 3 mo of 1997. When repeated, all laboratory data were averaged to provide a better estimate of exposure. No laboratory data during the 12- to 18-mo follow-up were used. The sample included 40,538 patients.

The primary *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for each hospitalization was recorded. Cardiovascular hospitalization incorporated the following ICD-9-CM codes: 390 to 459 (diseases of the circulatory system), 518.4 (acute pulmonary edema), 276.6 (fluid overload), 785 (symptoms involving cardiovascular system), 786.5 (chest pain), 780.2 (syncope and collapse), and 798 (sudden death). Infection-related hospitalization included the following ICD-9-CM codes: 001 to 139 (infectious and parasitic diseases), 320 to 324 (meningitis and encephalitis), 421 (endocarditis), 480 to 486 (pneumonia), 590 (infections of the kidney), 680 to 686 (infections of the skin and subcutaneous tissue), and 790.7 (bacteremia). Fracture-related hospitalization included ICD-9-CM codes 800 to 829. Vascular access–related (non–infection-related) hospitalization included ICD-9-CM codes 996.1, 996.70, 73, and 74.

Several confounding variables were included in the analyses. Age, gender, race or ethnicity, diabetes, and vintage (time since initiation of dialysis) were considered to represent "case mix." Laboratory variables included parameters of mineral metabolism (phosphorus, calcium, PTH, and aluminum), nutritional status (serum albumin, predialysis blood urea nitrogen [BUN], creatinine, cholesterol, and bicarbonate), and hematologic status (hemoglobin and ferritin). Body size was estimated using body weight, body surface area, or Quetèlet's (body mass) index. Dialysis dose was estimated using the urea reduction ratio (URR) or the indexed or nonindexed urea clearance × time product (Kt/V_{urea} and Kt_{urea}).

We *a priori* stratified serum phosphorus into 8 categories in 1.0-mg/dl increments (<3.0 to ≥9.0 mg/dl), serum calcium into 8 categories in 0.5-mg/dl increments (<8.0 to ≥11.0 mg/dl), and calcium-phosphorus product into 12 categories in 5-mg^2/dl^2 increments (<30 to ≥80 mg^2/dl^2). Serum calcium was adjusted for serum albumin according to an equation commonly used in the general population: adjusted calcium = measured calcium + [(4.0 − serum albumin in g/dl) × 0.8]. We also calculated an adjusted calcium using an equation validated in hemodialysis patients: adjusted calcium = measured calcium + [0.0176 × (34 − serum albumin in g/dl)] (15). We *a priori* stratified PTH concentrations into four categories representing relatively low (<150 pg/ml), target (150 to 300 pg/ml), mild to moderate (300 to 600 pg/ml), and moderate to severe (≥600 pg/ml) elevations in PTH. We further subdivided categories of phosphorus and PTH in secondary analyses. Where outcomes were relatively rare (*e.g.*, fracture-related hospitalizations), we considered companion models using continuous terms for phosphorus, calcium, and PTH.

Statistical Analyses

Continuous variables were expressed as mean ± SD or median with interquartile range and compared with parametric or nonparametric tests, where appropriate. Categorical variables were expressed as proportions and compared with the χ^2 test. Unadjusted, case mix–adjusted, and multivariable-adjusted survival analyses were performed using the proportional hazards regression model (16). Multivariable models were constructed with backward variable selection, using $P < 0.05$ for variable retention. Plots of log (-log [survival rate]) against log (survival time) were performed to establish the validity of the proportionality assumption (17). Effect modification was evaluated by including multiplicative interaction terms for selected variables. Factors not included in multivariable models were re-entered individually to evaluate for residual confounding (>10% change in the parameter estimate for phosphorus, calcium, or PTH). There were few missing laboratory data except for PTH (n = 5995, 14.8%), cholesterol (n = 13,613, 33.6%), and aluminum (n = 15,940, 39.3%). To avoid a significant loss of power, we included missing indicator variables in regression models. We calculated the population attributable risk percentage for selected factors, where prevalence in the exposed group was P_e using the formula $[P_e \times (RR - 1)]/([P_e \times (RR - 1)] + 1) \times 100$. Patients who underwent kidney transplantation (n = 1742, 4.3%), recovered renal function (n = 169, 0.4%), transferred dialysis facilities (n = 5598, 13.8%), withdrew from dialysis (n = 1173, 2.9%), or were lost to follow-up for unknown reasons (n = 64, 0.2%) were censored. Two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC).

Results

Table 1 summarizes the distribution of case mix and several laboratory variables stratified by categories of serum phosphorus. Age was inversely ($r = -0.30$) and vintage directly ($r = 0.11$) correlated with serum phosphorus concentration. Serum phosphorus was directly correlated with predialysis BUN, a proxy for dietary protein intake ($r = 0.33$); serum creatinine, a proxy for muscle mass ($r = 0.36$); and serum albumin ($r = 0.14$) and inversely correlated with serum bicarbonate, another proxy for dietary protein intake ($r = -0.37$).

Table 2 shows the analogous results stratified by categories of adjusted serum calcium. Age ($r = 0.13$) and vintage ($r = 0.09$) were directly correlated with adjusted serum calcium concentration. Black individuals were significantly more likely to have lower adjusted serum calcium concentrations. Serum calcium was inversely correlated with predialysis BUN ($r = -0.11$), serum creatinine ($r = -0.07$) and albumin ($r = -0.10$) and directly correlated with serum bicarbonate ($r = 0.26$; $P < 0.0001$ for all reported correlations owing to large sample size).

Relative Risks of Death

There were 10,015 deaths during the 12- to 18-mo follow-up, corresponding to an annual mortality rate of 19.5%.

Serum Phosphorus

Figure 1 shows the unadjusted, case mix–adjusted, and multivariable-adjusted relative risks (RR) and 95% confidence intervals (CI) associated with categories of serum phosphorus, considering phosphorus concentrations 4.0 to 5.0 mg/dl the referent range. The unadjusted results demonstrate a significant increase in RR associated with lower serum phosphorus concentrations (<4.0 mg/dl) and no specific trend with serum phosphorus concentrations rising above the normal range. With adjustment for case mix, we observed an increase in the RR of death with higher serum phosphorus concentrations, reflecting considerable confounding by age in particular. With multivariable adjustment, the heightened risk associated with lower serum phosphorus was attenuated (and no longer statistically

Table 1. Patient characteristics by serum phosphorus category[a]

	<3 mg/dl (n = 895)	3–4 mg/dl (n = 3860)	4–5 mg/dl (n = 8723)	5–6 mg/dl (n = 10,421)	6–7 mg/dl (n = 8367)	7–8 mg/dl (n = 4547)	8–9 mg/dl (n = 2219)	≥9 mg/dl (n = 1506)	P Value
Age (years)	67.3	66.4	64.6	61.9	58.6	55.3	52.1	48.7	<0.0001
Gender (% female)	53%	48%	50%	50%	48%	48%	46%	42%	<0.0001
Race/ethnicity (%)									<0.0001
white	27%	37%	39%	39%	35%	35%	37%	44%	
black	56%	45%	42%	41%	44%	44%	43%	36%	
Hispanic	14%	15%	15%	16%	17%	18%	17%	16%	
other	3%	3%	4%	3%	4%	4%	4%	3%	
Diabetes (%)	46%	48%	50%	49%	46%	43%	40%	35%	<0.0001
Vintage (years)	1.50	1.46	1.51	1.59	1.82	1.95	2.12	2.07	<0.0001
Weight (kg)	65.5	68.8	70.6	72.1	73.9	74.9	75.3	74.8	<0.0001
Quetèlet's (body mass) index (kg/m^2)	25.1	25.7	26.2	26.7	27.2	27.4	27.8	27.0	<0.0001
Bicarbonate (mEq/L)	23.3	22.6	21.9	21.2	20.6	19.9	19.2	18.1	<0.0001
BUN (mg/dl)	47	51	55	58	62	65	68	72	<0.0001
Creatinine (mg/dl)	7.7	8.0	8.5	9.3	10.3	11.0	11.6	12.2	<0.0001
Albumin (g/dl)	3.60	3.74	3.82	3.86	3.90	3.91	3.92	3.93	<0.0001
Cholesterol (mg/dl)	163	170	172	173	172	170	167	165	0.05
Hemoglobin (g/dl)	10.1	10.3	10.5	10.5	10.5	10.4	10.4	10.3	0.002
Ferritin (μg/L)	476	433	431	411	418	408	383	342	<0.0001
URR (%)	69.8%	69.5%	69.4%	68.9%	68.4%	67.7%	67.1%	65.9%	<0.0001

[a] Values are means; medians presented for vintage and ferritin. P values for proportions and means are age-adjusted. BUN, blood urea nitrogen; URR, urea reduction ratio.

Table 2. Patient characteristics by serum calcium category[a]

	<8.0 mg/dl (n = 2325)	8.0–8.5 mg/dl (n = 4594)	8.5–9.0 mg/dl (n = 10,451)	9.0–9.5 mg/dl (n = 10,759)	9.5–10.0 mg/dl (n = 6712)	10.0–10.5 mg/dl (n = 3652)	10.5–11.0 mg/dl (n = 1478)	≥11.0 mg/dl (n = 567)	P Value
Age (years)	52.3	58.4	60.5	61.6	62.1	61.9	61.2	62.3	<0.0001
Gender (% female)	39%	41%	46%	50%	53%	56%	54%	60%	<0.0001
Race/ethnicity (%)									<0.0001
white	23%	31%	37%	40%	40%	43%	41%	41%	
black	53%	44%	43%	42%	42%	40%	41%	37%	
Hispanic	20%	21%	17%	15%	13%	13%	13%	18%	
other	4%	4%	3%	3%	4%	4%	5%	4%	
Diabetes (%)	39%	49%	50%	48%	44%	41%	38%	40%	<0.0001
Vintage (years)	2.5	1.9	2.0	2.4	2.5	2.5	2.5	2.5	<0.0001
Weight (kg)	75.4	73.5	72.5	72.4	71.6	70.5	69.6	69.9	<0.0001
Quetèlet's (body mass) index (kg/m^2)	27.3	26.9	26.7	26.8	26.5	26.1	25.9	25.9	<0.0001
Bicarbonate (mEq/L)	19.0	20.0	20.7	21.2	21.6	21.9	22.4	22.5	<0.0001
BUN (mg/dl)	66	61	59	58	59	58	57	55	<0.0001
Creatinine (mg/dl)	11.4	9.9	9.3	9.3	9.7	9.7	9.8	9.1	<0.0001
Albumin (g/dl)	3.96	3.92	3.86	3.83	3.84	3.84	3.79	3.66	<0.0001
Cholesterol (mg/dl)	165	169	171	172	172	172	170	171	<0.0001
Hemoglobin (g/dl)	10.3	10.4	10.4	10.5	10.5	10.5	10.5	10.3	<0.0001
Ferritin (μg/L)	349	367	415	415	445	455	484	488	<0.0001
URR (%)	66.2%	67.5%	68.2%	68.9%	69.6%	69.8%	69.6%	70.0%	<0.0001

[a] Values are means, medians presented for vintage and ferritin. P values for proportions and means are age-adjusted.

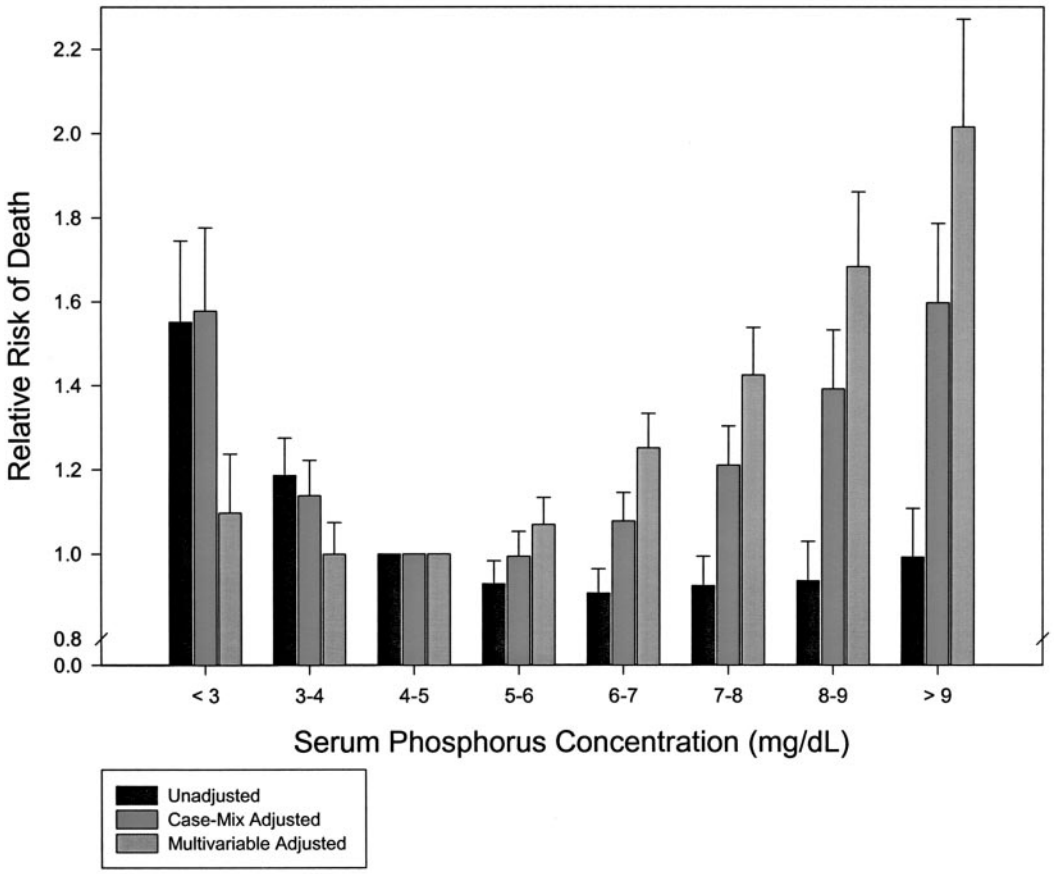

Figure 1. Unadjusted, case mix–adjusted, and multivariable-adjusted relative risks (RR; of death) and 95% confidence intervals (CI) for eight categories of serum phosphorus (referent range, 4.0 to 5.0 mg/dl). For all analyses, case mix adjustment refers to adjustment for age, gender, race or ethnicity, diabetes, and vintage. Multivariable adjustment refers to case mix plus body weight, URR*, serum albumin, creatinine, predialysis BUN*, bicarbonate*, cholesterol, hemoglobin, ferritin*, and aluminum. Phosphorus models simultaneously adjusted for calcium + parathyroid hormone (PTH), calcium models simultaneously adjusted for phosphorus + PTH, PTH models simultaneously adjusted for phosphorus + calcium. *Inclusion of linear and quadratic terms. Categories of vintage <2 yr (referent), 2 to 5 yr, ≥5 yr, and missing. Categories of cholesterol <120, 120 to 160, 160 to 200 (referent), 200 to 240, ≥240 mg/dl, and missing. Companion models substituting body surface area, Quetèlet's index, or calculated total body water for body weight, and Kt/V or Kt for URR did not change parameter estimates for phosphorus, calcium, or PTH.

significant), and the risk associated with higher serum phosphorus was accentuated. Higher serum phosphorus concentrations (≥11.0 mg/dl) were associated with even larger increases in RR (2.47; 95% CI, 1.90 to 3.19). Moreover, serum phosphorus concentrations elevated just above the 3.0- to 5.0-mg/dl range were associated with significant increases in RR. The RR were 1.10 (1.02 to 1.17) and 1.25 (1.18 to 1.33) for serum phosphorus concentrations 5.0 to 5.5 mg/dl and 5.5 to 6.0 mg/dl, respectively.

There was an interaction between the serum phosphorus concentration and diabetes, such that the RR associated with elevated serum phosphorus tended to be more pronounced among patients with diabetes, as was the RR associated with serum phosphorus <3.0 mg/dl (interaction term for curvilinear association, $P = 0.008$). The RR associated with hyperphosphatemia were otherwise independent of age, gender, race, and vintage.

Measured and Adjusted Serum Calcium

Figures 2 and 3 show unadjusted, case mix–adjusted, and multivariable-adjusted RR and 95% CI associated with categories of serum calcium, considering calcium concentrations 9.0 to 9.5 mg/dl the referent range. For measured serum calcium (Figure 2), the unadjusted and case mix–adjusted RR of death for serum calcium concentrations <8.5 mg/dl were significantly increased. These relations were reversed with multivariable adjustment, owing in part to the strong association between measured serum calcium and albumin ($r = 0.29$). The albumin-adjusted serum calcium concentration (Figure 3) was directly related to mortality, with a monotonic increase in risk observed across calcium categories. Results obtained using a hemodialysis-specific equation for adjustment of serum calcium were virtually identical, as were results in a subcohort of patients in whom ionized calcium was obtained (data not shown).

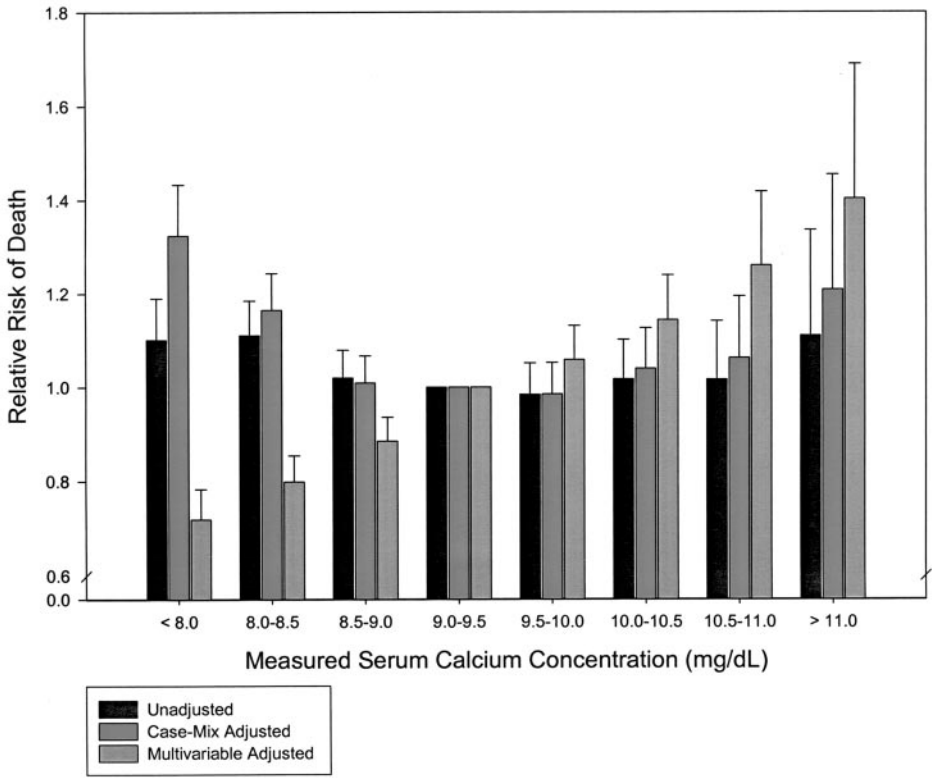

Figure 2. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for eight categories of measured serum calcium (referent range, 9.0 to 9.5 mg/dl).

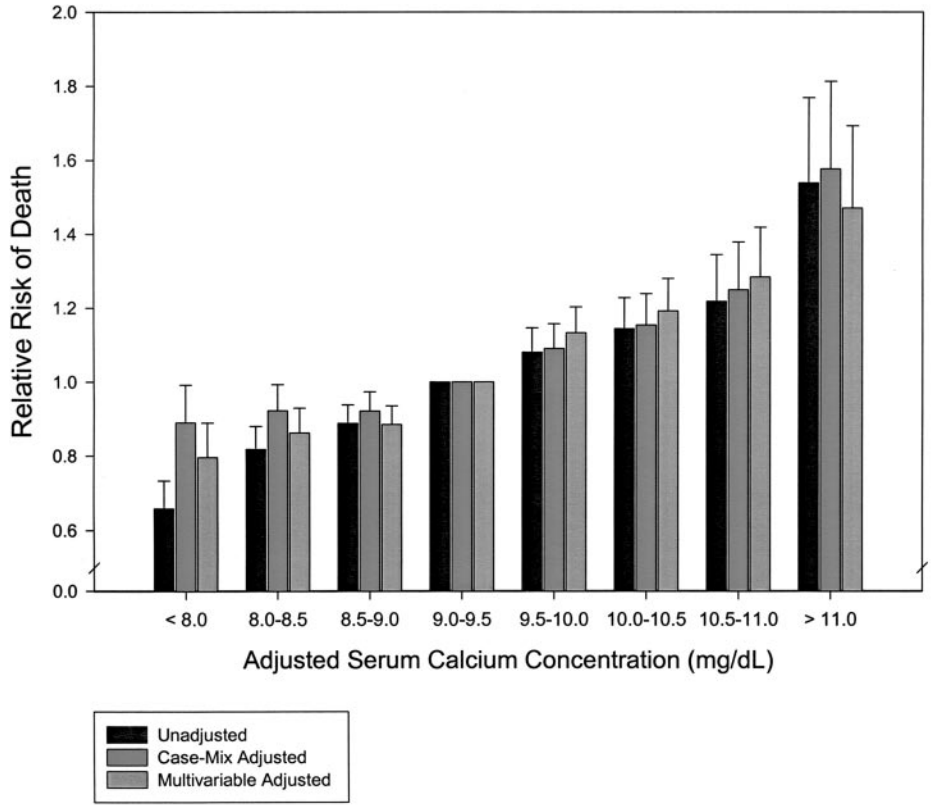

Figure 3. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for eight categories of adjusted serum calcium (measured calcium adjusted for serum albumin, referent range, 9.0 to 9.5 mg/dl).

Because serum calcium concentrations tend to rise with lower and decline with higher serum phosphorus concentrations, we performed secondary analyses fixing the serum phosphorus concentration within a relatively narrow range. We examined the relation between serum calcium and mortality within the four largest categories of serum phosphorus: 4.0 to 5.0, 5.0 to 6.0, 6.0 to 7.0, and 7.0 to 8.0 mg/dl. There was a significant increase in risk associated with higher adjusted serum calcium concentrations (linear estimates 1.25, 1.20, 1.19, and 1.18 per mg/dl increase; $P < 0.0001$) within each stratum of serum phosphorus. Significant increases in RR with higher adjusted serum calcium concentrations were observed even among patients whose phosphorus concentrations were <4.0 mg/dl. Higher serum calcium concentration was associated with mortality across the spectrum of PTH (adjusted calcium × PTH interaction, $P = 0.88$). The RR associated with higher serum calcium concentrations were also independent of age, gender, race, diabetes, and vintage.

Calcium × Phosphorus Product

Figure 4 shows unadjusted, case mix–adjusted, and multivariable-adjusted RR and 95% CI associated with categories of calcium × phosphorus product, considering values 40 to 45 mg^2/dl^2 the referent range. Multivariable RR associated with calcium-phosphorus products of 45 to 50 and 50 to 55 mg^2/dl^2 were 1.06 (0.98 to 1.15) and 1.14 (1.05 to 1.23), respectively. No further lowering of risk was observed with calcium × phosphorus products <45 mg^2/dl^2.

PTH

Figure 5 shows unadjusted, case mix–adjusted, and multivariable-adjusted RR and 95% CI associated with categories of intact PTH, considering values 150 to 300 pg/ml the referent range. Unadjusted results show an increase in the RR of death for patients with relatively low PTH (<150 pg/ml) and a decrease in RR for patients with higher PTH (300 to 600 and ≥600 pg/ml), the latter of borderline statistical significance. The adjusted results show an increase in the RR of death among patients with PTH ≥600 pg/ml, with the change in risk profile largely explained by confounding by case mix. PTH was significantly higher among younger patients, women, black individuals, and patients without diabetes, factors associated with enhanced survival. The association between PTH and survival was independent of age, gender, race, diabetes, and vintage. Companion models in which the higher range of PTH was subdivided by 300-pg/ml increments showed RR of 1.08 (0.97 to 1.20), 1.18 (1.03 to 1.35), and 1.24 (1.09 to 1.41)

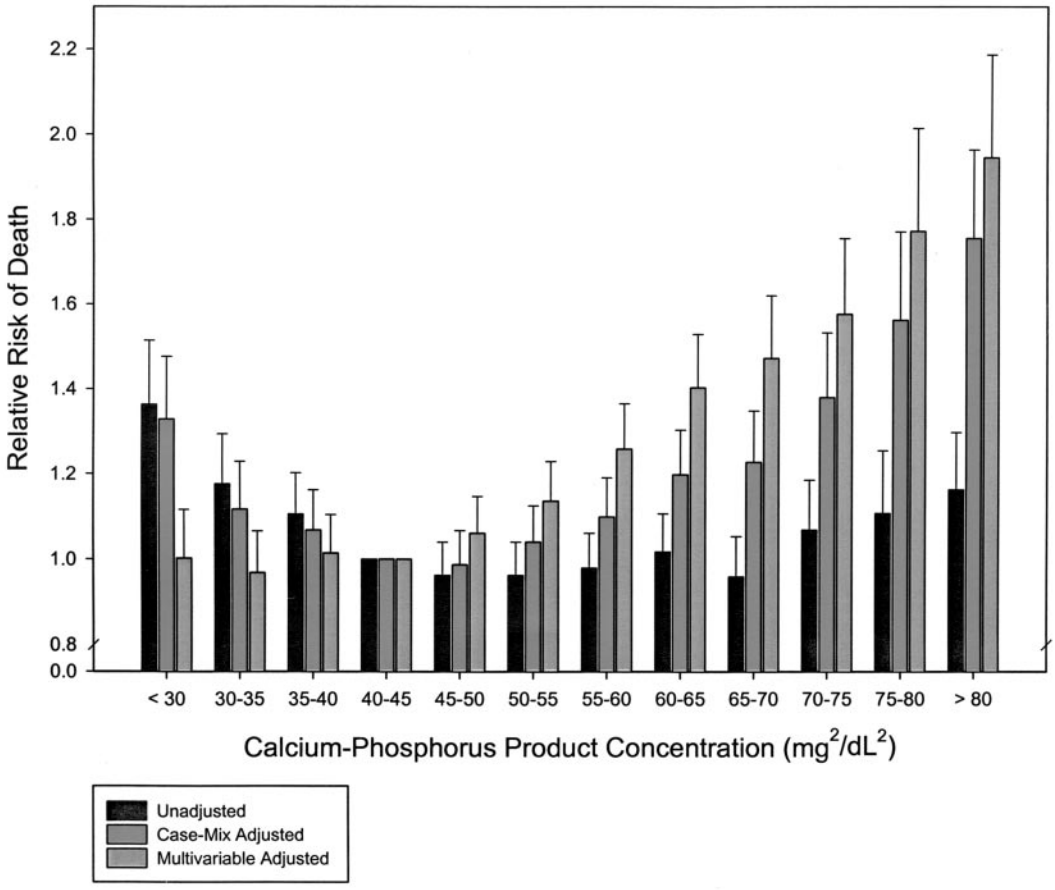

Figure 4. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for 12 categories of calcium × phosphorus product (referent range, 40 to 45 mg^2/dl^2).

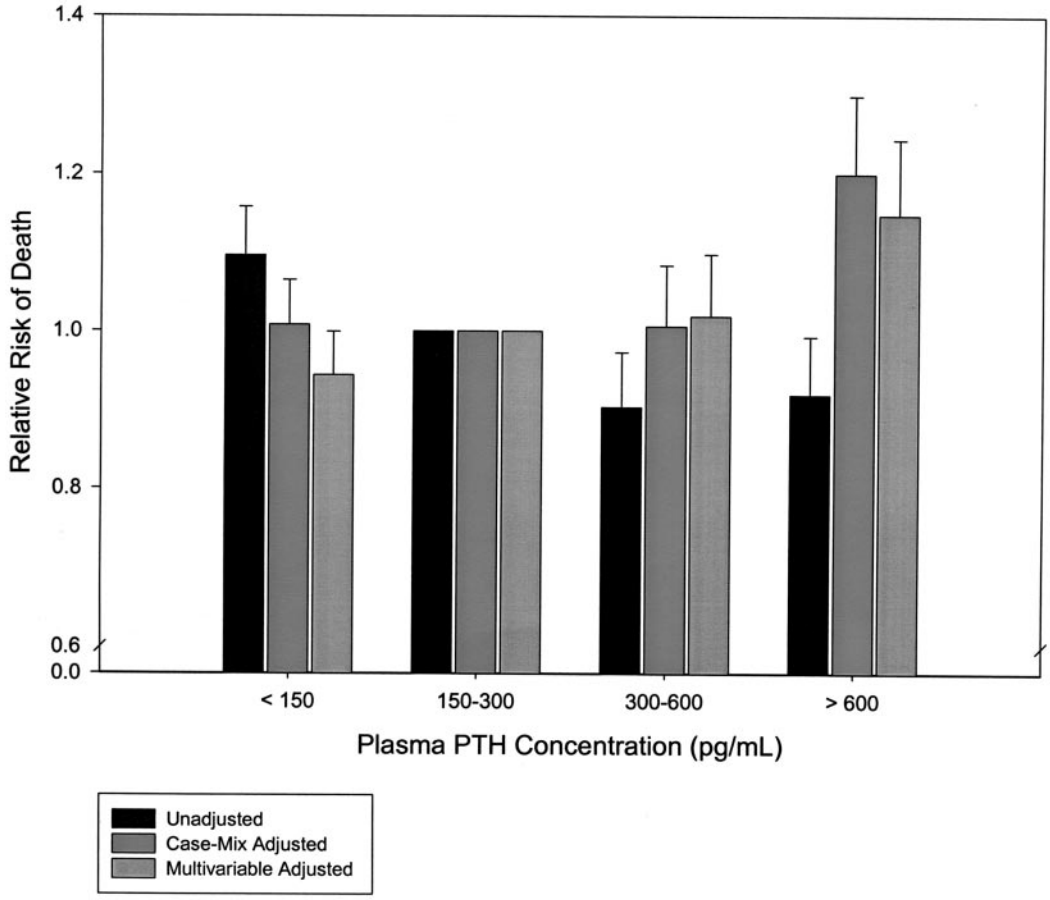

Figure 5. Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for four categories of intact parathyroid hormone (referent range, 150 to 300 pg/ml).

for patients with PTH 600 to 900, 900 to 1200, and ≥1200 pg/ml, respectively.

Population Attributable Risk Percentage

To compare the relative importance of disorders of mineral metabolism with other potentially mutable risk factors in hemodialysis patients, we calculated the population attributable risk percentage for several laboratory abnormalities. We considered hyperphosphatemia (defined as serum phosphorus ≥5.0 mg/dl), hypercalcemia (defined as serum calcium ≥10 mg/dl), and moderate to severe hyperparathyroidism (defined as PTH ≥600 pg/ml) individually and in combination. We compared these with population attributable risk percentages for inefficient dialysis (defined as URR <65%) and anemia (defined as hemoglobin <11 g/dl). The attributable risk associated with disorders of mineral metabolism (17.5%) was higher than that associated with inefficient dialysis (5.1%) or anemia (11.3%).

RR of Hospitalization

During the 12- to 18-mo follow-up period, 24,381 (60%) patients had one or more hospitalizations. Table 3 shows the 20 most common primary ICD-9-CM codes for initial hospitalizations.

All-Cause Hospitalization. Serum phosphorus, calcium, calcium × phosphorus product, and PTH were significantly associated with all-cause hospitalization on multivariable analysis. Compared with the 4.0- to 5.0-mg/dl referent group, the risk of all-cause hospitalization was increased by 4, 9, 18, 20, and 31% for patients with 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. The association between serum calcium and all-cause hospitalization was statistically significant but weak (RR, 1.04; 95% CI, 1.02 to 1.05 per mg/dl). PTH ≥600 pg/ml was significantly associated with hospitalization risk (RR, 1.07; 95% CI, 1.02 to 1.13). Secondary analyses suggested that the risk was driven by the fraction of patients ($n = 1252$, 3%) with PTH ≥1200 pg/ml (RR, 1.16; 95% CI, 1.07 to 1.25). Significant increases in all-cause hospitalization risk were seen for patients with calcium × phosphorus product ≥50 mg^2/dl^2.

Cardiovascular Hospitalization. There were 5876 cardiovascular hospitalizations recorded. The risk of cardiovascular hospitalization was increased by 10, 15, 29, 28, and 38% for patients with 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. There was no association between measured, adjusted, or ionized serum calcium and the risk of cardiovascular hospitalization. PTH ≥600 pg/ml was associated with a significantly increased risk of

Table 3. Twenty most common primary ICD-9-CM codes[a]

Diagnosis Code	Description	*N*	% of First Hospitalizations
996.1	Mechanical complication of other (noncardiac) vascular device, implant, and graft	2423	9.8%
585	Chronic renal failure	2132	8.6%
996.70, 73, and 74	Other complications of internal prosthetic device, implant, and graft	1401	5.6%
480–486	Pneumonia	1086	4.4%
276.6	Fluid overload	824	3.3%
428	Congestive heart failure	815	3.3%
786.5	Chest pain	752	3.0%
038.9	Unspecified septicemia	630	2.5%
578	Gastrointestinal hemorrhage	356	1.4%
999.9	Other and unspecified complications of medical care	271	1.1%
681–682	Cellulitis and abscess	258	1.0%
443	Peripheral vascular disease	239	1.0%
427.5	Cardiac arrest	231	0.9%
996.62	Infection and inflammatory reaction as a result of other (noncardiac) vascular device, implant, and graft	228	0.9%
787.01	Nausea with vomiting	205	0.8%
410	Acute myocardial infarction	198	0.8%
413	Angina pectoris	171	0.7%
780.6	Fever	156	0.6%
785.4	Gangrene	128	0.5%
251.2	Hypoglycemia	103	0.4%

[a] ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification.*

cardiovascular hospitalization (RR, 1.17; 95% CI, 1.06 to 1.29). Secondary analyses suggested that the risk was borne largely by the fraction of patients ($n = 2473$, 6%) with PTH ≥900 pg/ml (RR, 1.26; 95% CI, 1.12 to 1.42). As with all-cause hospitalization, the associations of calcium × phosphorus product with cardiovascular hospitalization mirrored those of phosphorus.

Advanced age, white race, and diabetes were significantly associated with cardiovascular hospitalization, as were lower body weight, higher concentrations of bicarbonate and ferritin, and lower concentrations of serum albumin and hemoglobin. As in the general population, total cholesterol was directly related to the risk of hospitalization for cardiovascular disease. Compared with the 160- to 200-mg/dl referent category, the RR of cardiovascular hospitalization was 0.85 (95% CI, 0.75 to 0.96) and 0.90 (95% CI, 0.83 to 0.97) for total cholesterol <120 and 120 to 160 mg/dl, respectively.

Infection-Related Hospitalization. There were 1386 hospitalizations as a result principally of infection. There were no significant associations among infection-related hospitalization and serum phosphorus, serum calcium, calcium × phosphorus product, or PTH. The risk of hospitalization as a result of infection was significantly increased with advanced age and dialysis vintage and decreased with black race; higher body weight; higher concentrations of serum albumin, creatinine, and hemoglobin; and lower concentrations of bicarbonate (proxies of nutritional status).

Fracture-Related Hospitalization. The serum phosphorus concentration was significantly related to hospitalization for fracture ($n = 257$) with a RR of 1.12 (95% CI, 1.03 to 1.22) per mg/dl increase in serum phosphorus. As expected, advanced age, female gender, white race, and lower body weight were significantly associated with an increased risk of fracture-related hospitalization. Dialysis vintage of 2 to 5 yr and ≥5 yr were strongly associated with fracture-related hospitalization (RR, 1.68; 95% CI, 1.22 to 2.31 and RR, 2.32; 95% CI, 1.48 to 3.62, compared with dialysis vintage <2 yr). Among laboratory variables other than phosphorus, only serum creatinine and total cholesterol were associated with fracture-related hospitalization. Fracture risk was lower with higher serum creatinine (RR, 0.89; 95% CI, 0.83 to 0.94 per mg/dl) and among the fraction of patients with total cholesterol <120 mg/dl (RR, 0.30; 95% CI, 0.12 to 0.74, compared with the 160- to 200-mg/dl referent category). PTH was directly associated with the risk of fracture-related hospitalization, albeit weakly ($P = 0.035$). There was no association between measured, adjusted, or ionized calcium and the risk of fracture-related hospitalization.

Vascular Access–Related Hospitalization. Finally, we examined the associations among parameters of mineral metabolism and vascular access–related (non–infection-related) hospitalization ($n = 3824$). Serum phosphorus and calcium were unrelated to vascular access–related hospitalization. Higher PTH was associated with a slightly lower risk of vascular access–related hospitalization ($P = 0.008$). The major

predictors of vascular access–related hospitalization were female gender, nonwhite race, higher body weight, and lower serum albumin. As expected, vascular access–related hospitalizations were associated with higher predialysis BUN and lower URR.

Discussion

Patients on hemodialysis experience mortality rates in excess of 20% per year, a phenomenon driven largely by a 30- to >100-fold increase in age-, gender-, and race-adjusted cardiovascular mortality rates, depending on age (18). Previous reports have identified associations among certain disorders of mineral metabolism and all-cause and cardiovascular mortality. Pooling two random samples of prevalent US hemodialysis patients evaluated during the early 1990s, US Renal Data System investigators showed a 27% increase in the RR of death associated with a serum phosphorus >6.5 mg/dl and a 34% increase in RR associated with calcium-phosphorus product >72 mg^2/dl^2 (19). Using the same data source, serum phosphorus >6.5 mg/dl was found to be significantly associated with sudden death and death as a result of coronary artery disease; moderate to severe hyperparathyroidism (PTH >495 pg/ml) was weakly associated with sudden death (20). In the current study, we confirm and extend these findings. A more contemporary cohort, larger sample size, more frequent laboratory determinations, and wider array of covariates (including multiple parameters of nutritional status) allowed for a more detailed exploration of the relations among disorders of mineral metabolism, mortality, and morbidity (including cause-specific hospitalization).

As expected, markers of nutritional status were directly correlated with serum phosphorus. Thus, improved nutritional status might explain the absence of a higher risk of death associated with hyperphosphatemia in unadjusted analyses or the crude association between hyperparathyroidism and survival shown in Figure 4 and reported independently by Avram *et al.* (21).

A direct relation between higher serum calcium concentrations and an increased RR of death was observed across the entire spectrum of serum calcium independent of age, race, gender, diabetes, vintage, phosphorus, and PTH. These results contrast with those reported by Foley *et al.* (22), where in a single-center study, serum calcium <8.8 mg/dl was associated with increased mortality. In the US Renal Data System study cited above (19), there was no association between calcium and mortality, although the sample size was relatively small and only a single determination of serum calcium was used. We also examined the risks of higher serum calcium concentrations within narrowly fixed, clinically relevant ranges of serum phosphorus. A robust and consistent increase (~20% increase in RR per mg/dl increase in serum calcium) was observed with higher serum calcium within each mg/dl stratum of serum phosphorus.

Although we identified an association between higher PTH and mortality when adjusting for case mix and other laboratory variables, the RR was driven principally by patients with PTH ≥900 pg/ml. Although hyperparathyroidism may be associated with considerable morbidity (*e.g.*, bone pain, fractures, anemia, hypertension, pruritus, sexual dysfunction) (23), the PTH-mortality relation seems weaker than the phosphorus-mortality or calcium-mortality relations described herein. Differential misclassification could explain some of the difference in RR. Regardless, treatment strategies that focus primarily on PTH reduction without due consideration for the effects of treatment on the concentrations of phosphorus and calcium may be ill advised.

The mechanisms underlying the increase in mortality and morbidity associated with disturbances in mineral metabolism remain speculative. Several reports have described the ability of serum phosphorus to potently stimulate the phenotypic transformation of vascular smooth muscle cells into osteoblasts capable of producing a pro-mineralizing milieu (24,25). In this environment, supersaturation of extracellular calcium and phosphorus may accelerate the development of medial wall vascular calcification, a pathologic process known to be associated with increases in arterial stiffness, aortic pulse wave velocity, left ventricular size, and all-cause mortality in patients on hemodialysis (26). In addition, visceral myocardial calcification may enhance the risk of arrhythmic events and sudden death, the most common single cause of cardiovascular death in this population. Previous studies have demonstrated associations among disorders of mineral metabolism and vascular calcification (27,28). Increased risks of death and cardiovascular hospitalization with hyperphosphatemia and hyperparathyroidism are consistent with these observations.

Other predictors of death and hospitalization in this cohort were generally consistent with previously published reports (29,30). The direct association between total cholesterol and the risk of cardiovascular hospitalization was noteworthy, given the paradoxical association between total cholesterol and all-cause mortality described in several studies of dialysis patients (31,32). Few previous studies of dialysis patients have examined the risk of fracture, a relatively rare reason for hospitalization. Coco and Rush (33) showed an increased risk of fracture with lower PTH concentrations, although these results were not adjusted for age, gender, race, or other factors jointly associated with PTH and fracture risk. Using data from the DMMS Wave 1, Stehman-Breen *et al.* (34) found advanced age, female gender, and white race to be significantly associated with hip fracture, as we also demonstrated. The inverse relations among serum creatinine, body weight, and fracture risk are also consistent with published reports that physical activity (muscle mass) and weight bearing reduce the risk of fractures in nonuremic individuals (35,36). We were interested to observe the association between low total cholesterol and reduced fracture risk. Whether this finding is directly related to the cholesterol concentration, indirectly related to the use of HMG-CoA reductase inhibitors ("statins") (37), or a chance observation is unknown.

There are several limitations to our analysis. First, some unmeasured confounding variables might be expected to dampen and others enhance the RR described here. For instance, behaviors associated with poor adherence might be jointly associated with hyperphosphatemia and higher risks of death and hospitalization. Conversely, more robust lean body

mass and higher dietary energy intake might be jointly associated with hyperphosphatemia and lower risks of death and hospitalization. Although adjustment for additional covariates (*e.g.*, markers of inflammation and oxidative stress, interdialytic weight gain, psychologic well-being) might further refine RR estimates, we would be unlikely to extinguish the RR observed in association with significant elevations in phosphorus and calcium. Second, the use of primary ICD-9-CM diagnosis codes limits the capacity to identify associations between disorders of mineral metabolism and cause-specific hospitalization. There may have been additional hospitalizations for cardiovascular disease or fracture that were not captured. In particular, hospitalizations coded with the primary ICD-9-CM code 585 (chronic renal failure) may have had informative secondary and tertiary ICD-9-CM codes. Third, the study sample was restricted to hemodialysis patients, so the associations described cannot be extrapolated to peritoneal dialysis patients or to people with less severe degrees of chronic kidney disease. Finally, although we would expect that the hazards associated with hyperphosphatemia, hypercalcemia, and hyperparathyroidism would be diminished with correction of these abnormalities, we cannot conclude any definitive benefit absent an interventional trial.

In summary, using a nationally representative database of >40,000 hemodialysis patients, we identified strong associations among higher concentrations of serum phosphorus and calcium and an increased risk of death. Serum phosphorus concentrations associated with the lowest mortality rates were around the normal laboratory range and for calcium were around the low-normal laboratory range. There was also an association between the degree of secondary hyperparathyroidism and mortality, albeit weaker in magnitude. We also found that hyperphosphatemia and hyperparathyroidism were associated with all-cause hospitalization as well as with hospitalization for cardiovascular disease and fracture. These results collectively support the hypothesis that disorders of mineral metabolism contribute to the burden of cardiovascular disease in the ESRD population.

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