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Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study

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Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study.

Background. Altered mineral metabolism contributes to bone disease, cardiovascular disease, and other clinical problems in patients with end-stage renal disease.

Methods. This study describes the recent status, significant predictors, and potential consequences of abnormal mineral metabolism in representative groups of hemodialysis facilities ($N = 307$) and patients ($N = 17{,}236$) participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) in the United States, Europe, and Japan from 1996 to 2001.

Results. Many patients fell out of the recommended guideline range for serum concentrations of phosphorus (8% of patients below lower target range, 52% of patients above upper target range), albumin-corrected calcium (9% below, 50% above), calcium-phosphorus product (44% above), and intact PTH (51% below, 27% above). All-cause mortality was significantly and independently associated with serum concentrations of phosphorus (RR 1.04 per 1 mg/dL, $P = 0.0003$), calcium (RR 1.10 per 1 mg/dL, $P < 0.0001$), calcium-phosphorus product (RR 1.02 per 5 mg^2/dL^2, $P = 0.0001$), PTH (1.01 per 100 pg/dL, $P = 0.04$), and dialysate calcium (RR 1.13 per 1 mEq/L, $P = 0.01$). Cardiovascular mortality was significantly associated with the serum concentrations of phosphorus (RR 1.09, $P < 0.0001$), calcium (RR 1.14, $P < 0.0001$), calcium-phosphorus product (RR 1.05, $P < 0.0001$), and PTH (RR 1.02, $P = 0.03$). The adjusted rate of parathyroidectomy varied 4-fold across the DOPPS countries, and was significantly associated with baseline concentrations of phosphorus (RR 1.17, $P < 0.0001$), calcium (RR 1.58, $P < 0.0001$), calcium-phosphorus product (RR 1.11, $P < 0.0001$), PTH (RR 1.07, $P < 0.0001$), and dialysate calcium concentration (RR 0.57, $P = 0.03$). Overall, 52% of patients received some form of vitamin D therapy, with parenteral forms almost exclusively restricted to the United States. Vitamin D was potentially underused in up to 34% of patients with high PTH, and overused in up to 46% of patients with low PTH. Phosphorus binders (mostly calcium salts during the study period) were used by 81% of patients, with potential overuse in up to 77% patients with low serum phosphorus concentration, and potential underuse in up to 18% of patients with a high serum phosphorus concentration.

Conclusion. This study expands our understanding of the relationship between altered mineral metabolism and outcomes and identifies several potential opportunities for improved practice in this area.

Key words: mineral metabolism, vitamin D, phosphorus binders, calcium-phosphorus product, parathyroid hormone, DOPPS.

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End-stage renal disease (ESRD) is accompanied by profound changes in mineral metabolism. The laboratory manifestations include hypocalcemia, hyperphosphatemia, hypovitaminosis D, and hyperparathyroidism. Abnormal mineral metabolism leads to metabolic bone disease [1] and contributes to other clinical problems, such as muscle and joint disease, anemia, neuropathy, and impotence. The complex relationship between metabolic abnormalities and clinical disease confounds efforts to prioritize corrective interventions. Evidence-based guidelines have been developed to assist with treatment decisions. These guidelines propose target ranges for such indicators of mineral metabolism as serum calcium, phosphorus, and parathyroid hormone (PTH) concentrations. However, the evolving guidelines are often based on incomplete information. Although bone disease has been the traditional focus of concern, recent studies highlight the importance of other outcomes, particularly vascular disease and mortality. This paper describes the associations between mineral metabolic abnormalities and mortality for hemodialysis patients in 7 countries participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

METHODS

The study was done as part of the DOPPS, an international, observational study of hemodialysis practices and outcomes in countries with large populations of dialysis patients: France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States. The study design has been described previously [2]. Institutional Review Board approval and patient informed consent were obtained as required in each country. A representative sample of hemodialysis facilities was selected in each country (France, Germany, Italy, Spain, and the UK, $N = 20$ each; Japan, $N = 65$; U.S., $N = 142$). Patients were entered into the study from 1996 to 2001 in the U.S., from 1998 to 2000 in Europe, and from 1999 to 2000 in Japan. A random sample of patients was selected from each facility at the start of the study, representing a prevalent cross-section ($N = 8615$). As patients departed during the study (due to death, transplantation, withdrawal, transfer, or dialysis modality change), replacement patients were randomly selected ($N = 8621$) from the pool of patients new to the facility since the last sample selection. The initial cross-section sample of prevalent patients was used to describe patient characteristics, such as the distribution of laboratory values. The entire sample of 17,236 patients was used for statistical modeling.

Clinical data were abstracted from the medical record for each study patient using standardized questionnaires. Dialysis facility personnel, usually a dialysis nurse, performed data abstraction. Follow-up data were obtained at approximately 4-month intervals. The major outcomes for this study were all-cause mortality, cardiovascular mortality, and parathyroidectomy (PTX). Cardiovascular mortality included deaths attributed to acute myocardial infarction, atherosclerotic heart disease, cardiac arrhythmia, and cardiac arrest (causes unknown). The major predictor variables were baseline patient characteristics, baseline laboratory markers of mineral metabolism, and modifiable practice patterns related to management of mineral metabolism (vitamin D, phosphorus binder, dialysate calcium concentration). Only PTH concentration measurements obtained by way of intact molecule assay were used in these analyses.

Standard descriptive statistics were used to describe the baseline state of mineral metabolism at the patient level. Logistic regression models, accounting for facility clustering effects, were used to determine the predictors of laboratory values that fell out of the guideline range. The Cox proportional hazards model was used to study associations between mortality (all-cause and cardiovascular) and markers of mineral metabolism. Cox survival models were stratified by country and adjusted for age, gender, race, duration of ESRD, single-pool Kt/V, serum albumin, hemoglobin, dialysate calcium concentration, and 14 summary comorbid conditions present at study entry (coronary artery disease, congestive heart failure, other cardiac disease, hypertension, cerebrovascular disease, peripheral vascular disease, diabetes, lung disease, cancer (excluding skin), HIV/AIDS, gastrointestinal bleeding, neurologic disease, psychiatric disease, and recurrent cellulitis). In addition, models were simultaneously adjusted for laboratory measures related to mineral metabolism including serum concentrations of phosphorus, calcium, and intact PTH. Prospective PTX models were adjusted for country, age, gender, race, duration of ESRD, PTH, serum calcium, serum phosphorus, and prior PTX. Survival models accounted for facility clustering effects using robust standard estimates based on the sandwich estimator. Statistical analyses were performed using SAS software, version 8.2 (SAS Institute; Cary, NC, USA).

Table 1. Characteristics of study sample

Demographics	Frequency (%) or mean		
	Initial cross-section ($N = 8615$)	Replacement patients ($N = 8621$)	All patients ($N = 17{,}236$)
Age *mean years*	59.9	61.1	60.5
Duration of ESRD *mean years*	4.9	1.2	3.1
Male	56.8	57.9	57.4
Black	17.7	20.8	19.2
Cause of ESRD			
Diabetes	26.9	36.8	31.6
Hypertension	18.4	23.8	21.0
Glomerulonephritis	30.1	17.1	23.8
Other	24.7	22.3	23.5
Coronary heart disease	36.0	40.5	38.3
Congestive heart failure	29.6	38.0	33.8
Other cardiovascular disease	33.2	28.4	30.8
Hypertension	73.2	77.5	75.3
Cerebrovascular disease	15.5	16.7	16.1
Peripheral vascular disease	21.3	22.8	22.1
Diabetes	33.0	42.6	37.8
Lung disease	9.4	12.0	10.7
Cancer, other than skin	8.4	11.3	9.8
HIV/AIDS	0.6	1.0	0.8
Gastrointestinal bleeding	6.9	7.1	7.0
Neurologic disease	8.4	8.4	8.4
Psychiatric disorder	18.9	22.9	20.9
Recurrent cellulitis	7.5	7.0	7.3

RESULTS

Characteristics of study sample

Table 1 displays the characteristics of the initial prevalent cohort, the replacement patient cohort, and the overall sample. By design, the replacement patients were enriched with new ESRD patients, as illustrated by fewer prior years of ESRD. The replacement patient group was older and had a higher prevalence of comorbid conditions, particularly diabetes mellitus and cardiovascular diseases. The study cohort yielded 4565 deaths (crude rate = 18.3/100 patient-years), 2278 cardiovascular deaths

Table 2. Parathyroidectomy (PTX) by country at baseline and prospectively

Country	Baseline		Follow-up		
	Prevalence (%)	AOR (*P* value)	Number	Incidence (/100 pt-yrs)	RR (*P* value)
France ($N = 981$)	14.3	2.2 (<0.0001)	20	1.8	3.76 (<0.0001)
Germany ($N = 908$)	6.0	1.5 (0.11)	11	1.0	3.19 (0.02)
Italy ($N = 869$)	5.0	0.7 (0.25)	10	0.9	2.16 (0.08)
Japan ($N = 2784$)	4.1	0.4 (<0.0001)	26	0.6	1.07 (0.80)
Spain ($N = 936$)	5.7	1.1 (0.75)	16	1.5	4.06 (<0.0001)
UK ($N = 897$)	9.2	2.5 (<0.0001)	12	1.5	3.18 (0.01)
U.S. ($N = 9861$)	4.0	1.0 (ref)	70	0.5	1.0 (ref)

AOR, adjusted odds ratio of having had a PTX (yes vs. no) prior to study entry; RR, relative risk of having a PTX during study follow-up. Adjustments for both models included age, gender, race, and duration of ESRD; the follow-up model was also adjusted for prior PTX.

Table 3. Descriptive statistics of laboratory values related to mineral metabolism in an initial cross-section of hemodialysis patients

Serum value	Recommended range[a]	Mean (SD)	Median	% of patients	
				Below lower range limit	Above upper range limit
Phosphorus ($N = 8265$)	3.5–5.5 mg/dL	5.8 (1.8)	5.6	7.6	51.6
Japan ($N = 2132$)		5.8 (1.6)	5.7	5.8	53.6
Europe ($N = 2525$)		5.7 (1.9)	5.5	10.1	49.4
U.S. ($N = 3608$)		5.9 (1.9)	5.6	6.8	51.9
Albumin-corrected calcium ($N = 6898$)	8.4–9.5 mg/dL	9.6 (1.0)	9.5	9.3	50.2
Japan ($N = 1617$)		9.4 (1.0)	9.4	12.2	45.2
Europe ($N = 1720$)		9.7 (0.9)	9.6	7.2	55.6
U.S. ($N = 3561$)		9.6 (1.0)	9.5	9.1	49.9
Ca-P product ($N = 8070$)	<55 mg^2/dL^2	54 (17)	53	NA	43.5
Japan ($N = 2131$)		54 (16)	52	NA	43.2
Europe ($N = 2337$)		54 (19)	53	NA	43.2
U.S. ($N = 3602$)		54 (17)	53	NA	43.8
PTH ($N = 5240$)	150–300 pg/mL	274 (400)	144	51.1	26.7
Japan ($N = 1142$)		196 (241)	111	58.6	19.0
Europe ($N = 1716$)		269 (365)	149	50.1	26.9
U.S. ($N = 2382$)		316 (473)	158	48.2	30.3

Initial cross-section taken at study start (1996 in the U.S., 1998 in Europe, 1999 in Japan).
[a] According to NKF K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease [5].

(crude rate = 10.0/100 patient-years) and 165 parathyroidectomies (crude rate = 0.7/100 patient-years). Country differences in mortality rates and comorbidities in the DOPPS have been described previously [3, 4]. PTX practice varied by country, as measured by the baseline prevalence of prior PTX (Table 2). Similarly, the prospective rate of PTX during follow-up varied 4-fold across countries (Table 2).

Phosphorus

The serum phosphorus concentration and its substantial deviation from guidelines among the prevalent patient sample are shown in Table 3. Only 41% of this cross-section of patients was found to have a serum phosphorus concentration within the range recommended by U.S. (NKF K/DOQI^{TM}) [5] and European (EBPG) [6] guidelines. More than half the patients exceeded the recommended level of 3.5 to 5.5 mg/dL. Table 4 shows that a serum phosphorus below the target range (<3.5 mg/dL) was significantly more likely in patients with low serum albumin concentration, older age, and higher dialysate calcium. A serum phosphorus concentration above the target range (>5.5 mg/dL) was inversely associated with age, black race, dialysis dose, and treatment in Italy; it was directly associated with the serum albumin concentration and treatment in Germany. All-cause and cardiovascular mortality were significantly associated with the serum phosphorus concentration (Table 5). Figure 1 shows that the relationship between all-cause mortality and serum phosphorus was bimodal with significantly higher risk of death for patients with serum phosphorus levels below 3.5 mg/dL (affecting 10% of patients) and above 6.5 mg/dL (affecting 29% of patients). The relative rate of new PTX was also associated with higher serum phosphorus concentration (Table 5).

Calcium

Table 3 shows the distribution of the serum total calcium concentration (corrected for serum albumin concentration) relative to recent guidelines. The serum calcium concentration was below the lower recommended range limit (<8.4 mg/dL) in 9.3% of patients, and above the upper range limit (>9.5 mg/dL) in 50% of patients. A serum calcium concentration below the target range was significantly more likely in males and in patients with higher serum albumin concentration (Table 4).

Table 4. Clinical and laboratory characteristics significantly associated with abnormal laboratory values

Lab abnormality	Inverse associations (less likely)	Direct associations (more likely)
Low serum phosphorus (<3.5 mg/dL)	Serum albumin (0.64 per 1 g/dL)	Age (1.01 per year) Dialysate Ca (1.40 per 1 mEq/L) Treated in UK (1.45)
High serum phosphorus (>5.5 mg/dL)	Age (0.98 per year) Black race (0.75) spKt/V (0.77 per 1 unit) Treated in Italy (0.65)	Serum albumin (1.26 per 1 g/dL) Treated in Germany (1.66)
Low albumin-corrected calcium (<8.4 mg/dL)	Age (0.99 per year) Duration of ESRD (0.96 per year) Hemoglobin (0.85 per 1 g/dL) Treated in UK (0.58)	Male sex (1.25) Serum albumin (1.83 per 1 g/dL)
High albumin-corrected calcium (>9.5 mg/dL)	Male sex (0.74) Diabetes (0.77) Serum albumin (0.63 per 1 g/dL)	Duration of ESRD (1.07 per year) Hemoglobin (1.13 per 1 g/dL) spKt/V (1.40 per 1 unit) Other cardiac disease (1.15) Recurrent cellulitis (1.27) Treated in: Spain (1.54) UK (2.04)
Low PTH (<150 pg/mL)	Black race (0.64) Vitamin D therapy (0.82)	Dialysate Ca (1.31 per 1 mEq/L)
High PTH (>300 pg/mL)	Age (0.99 per year) Male sex (0.85) Hemoglobin (0.93 per 1 g/dL) spKt/V (0.56 per 1 unit) Diabetes (0.65) HIV (0.33) Treated in Japan (0.37)	Black race (1.45) Duration of ESRD (1.04 per year) Vitamin D therapy (1.31)

Adjusted odds ratios (AOR) given in parentheses. Models adjusted for age, gender, race, duration of ESRD, vitamin D use, dialysate calcium concentration, hemoglobin, albumin, Kt/V, country, and 14 summary comorbid conditions. Reference group = lab values in target range [5, 6]. All associations listed are significant at $P < 0.01$ level.

Table 5. Association between study outcomes (all-cause mortality, cardiovascular mortality, and parathyroidectomy) and markers of mineral metabolism

	RR (95% CI) *P* value		
Baseline lab measure	All-cause mortality[a]	Cardiovascular mortality[a]	Risk of new parathyroidectomy[b]
Phosphorus (per 1mg/dL)	1.04 (1.02–1.06) *0.0003*	1.09 (1.05–1.12) *<0.0001*	1.17 (1.09–1.25) *<0.0001*
Albumin-corrected calcium (per 1 mg/dL)	1.10 (1.06–1.15) *<0.0001*	1.14 (1.07–1.21) *<0.0001*	1.58 (1.35–1.85) *<0.0001*
Calcium-phosphorus product (per 5 mg^2/dL^2)	1.02 (1.02–1.03) *0.0001*	1.05 (1.05–1.05) *<0.0001*	1.11 (1.10–1.12) *<0.0001*
PTH (per 100 pg/mL)	1.01 (1.00–1.02) *0.04*	1.02 (1.00–1.03) *0.03*	1.07 (1.05–1.09) *<0.0001*
Dialysate calcium (per 1 mEq/L)	1.13 (1.03–1.25) *0.01*	1.09 (0.92–1.30) *0.30*	0.57 (0.35–0.95) *0.03*

All models were adjusted for PTH, dialysate calcium, and either calcium and phosphorus as two independent variables or calcium-phosphorus product as one independent variable.
[a]Stratified by country and adjusted for age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and 14 summary comorbid conditions.
[b]Stratified by country and adjusted for age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and prior parathyroidectomy.

A serum calcium concentration below the target range was inversely associated with age, duration of ESRD, hemoglobin concentration, and treatment in the UK. A serum calcium concentration above the target range was significantly associated with clinical factors shown in Table 4. All-cause and cardiovascular mortality were significantly associated with the serum calcium concentration (Table 5, Fig. 2). Serum calcium concentrations below 7.8 mg/dL were associated with significantly lower mortality risk (Fig. 2). The risk of new PTX was strongly associated with the baseline serum calcium concentration (Table 5).

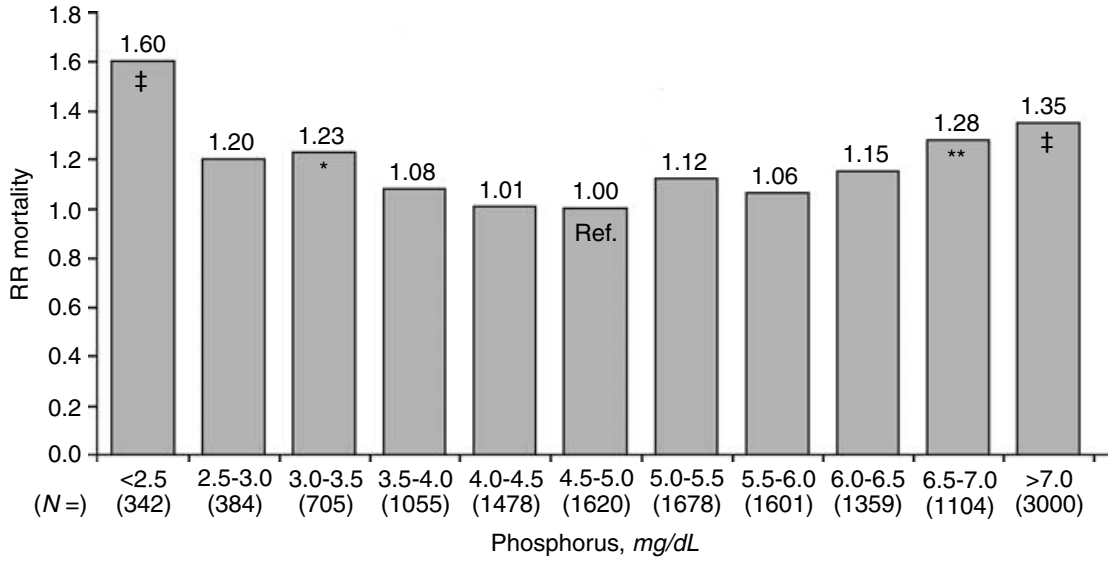

Fig. 1. Association between all-cause mortality and serum phosphorus concentration. Stratified by country and adjusted for serum concentrations of calcium and PTH, dialysate calcium concentration, age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and 14 summary comorbid conditions. $^{*}P < 0.05$; $^{**}P < 0.01$; †$P < 0.001$; ‡$P < 0.0001$.

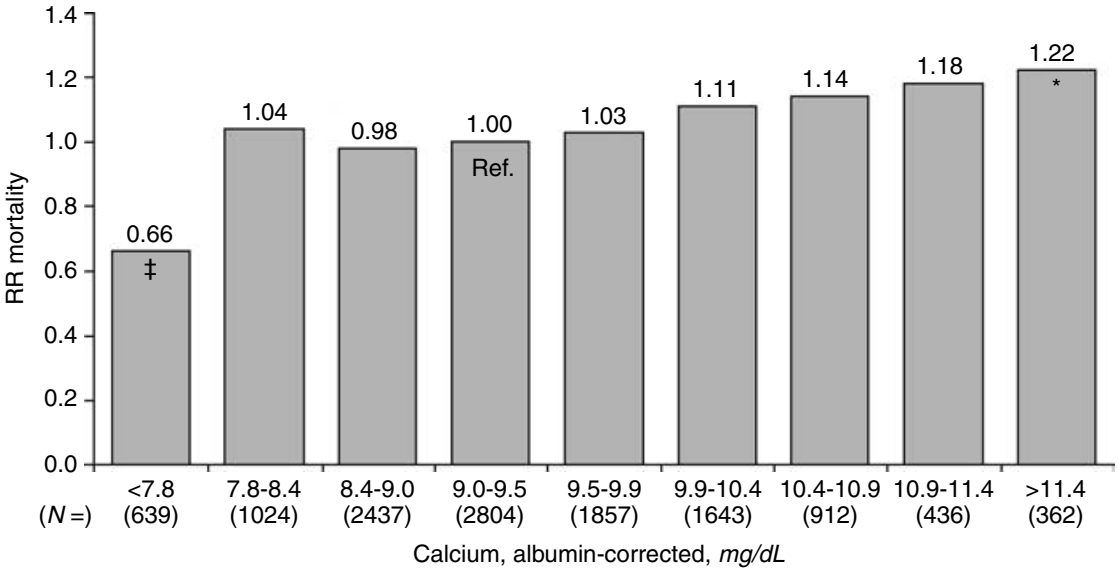

Fig. 2. Association between all-cause mortality and the serum concentration of calcium (corrected for albumin concentration). Stratified by country and adjusted for serum concentrations of phosphorus and PTH, dialysate calcium concentration, age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and 14 summary comorbid conditions. $^{*}P < 0.05$; $^{**}P < 0.01$; †$P < 0.001$; ‡$P < 0.0001$.

Calcium-phosphorus product

The average calcium-phosphorus product (not corrected for albumin) was 54 mg^2/dL^2, with approximately 44% of patients exceeding the recommended upper limit of 55 mg^2/dL^2. All-cause mortality, cardiovascular mortality, and parathyroidectomy risk were significantly associated with the calcium-phosphorus product (Table 5). Categorical analysis revealed a significantly increased mortality risk above a calcium-phosphorus product of approximately 65 mg^2/dL^2 (Fig. 3).

Parathyroid hormone

The prevalent patient cohort exhibited large variation in the serum intact PTH concentration, as illustrated by the large standard deviation (Table 3). The optimal range for PTH is considered to be 150 to 300 pg/mL [5, 6]. The PTH concentration was below 150 pg/mL in 51% of patients and above 300 pg/mL in 27% of patients. Table 4 shows that low PTH (<150 pg/dL) was directly associated with the dialysate calcium concentration and inversely associated with black race and vitamin D therapy.

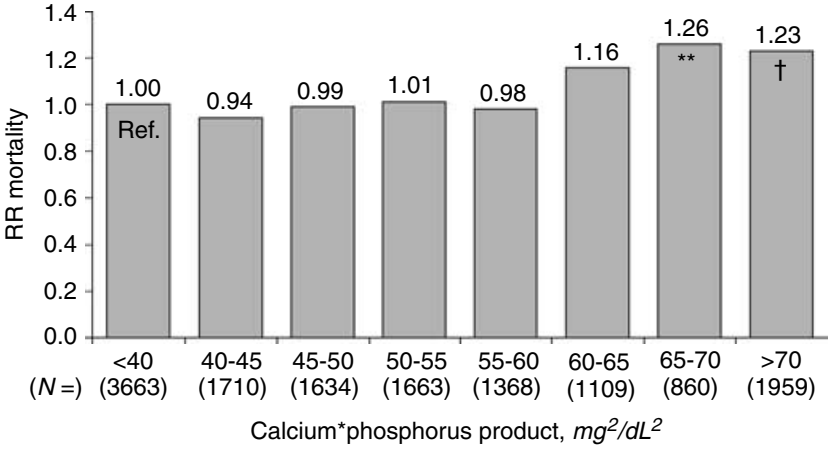

Fig. 3. Association between all-cause mortality and serum calcium-phosphorus product. Stratified by country and adjusted for serum concentration of PTH, dialysate calcium concentration, age, gender, race, duration of ESRD, hemoglobin, albumin, Kt/V, and 14 summary comorbid conditions.*$P <$ 0.05; **$P < 0.01$; †$P < 0.001$; ‡$P < 0.0001$.

Table 6. Facility distribution of practice patterns related to mineral metabolism (initial cross section)

Practice	% Patients	Facility distribution by percentile		
		25th	50th	75th
Vitamin D therapy ($N_1 = 8615$; $N_2 = 307$)	52.2	36.8	51.4	66.7
Japan ($N_1 = 2169$; $N_2 = 64$)	62.9	50.0	61.3	79.5
Europe ($N_1 = 2590$; $N_2 = 101$)	46.5	30.8	46.2	59.1
U.S. ($N_1 = 3856$; $N_2 = 142$)	50.0	36.0	50.0	65.5
Phosphorus binder ($N_1 = 8615$; $N_2 = 307$)	81.1	76.7	86.2	92.6
Japan ($N_1 = 2169$; $N_2 = 64$)	82.0	75.9	88.5	93.8
Europe ($N_1 = 2590$; $N_2 = 101$)	77.3	70.2	81.4	91.8
U.S. ($N_1 = 3856$; $N_2 = 142$)	83.1	80.0	87.5	92.3
Low dialysate calcium (≤2.5 mEq/L) ($N = 7629$; $N = 307$)	40.5	0.0	24.3	96.3
Japan ($N = 2123$; $N = 64$)	19.8	0.0	0.0	9.1
Europe ($N = 1839$; $N = 101$)	23.9	0.0	4.5	42.3
U.S. ($N = 3,667$; $N = 142$)	64.1	25.6	89.4	100.0

N_1 = patients; N_2 = facilities. Initial cross-section taken at study start (1996 in the U.S., 1998 in Europe, 1999 in Japan.

In contrast, high PTH (>300 pg/dL) was directly associated with black race, duration of ESRD, and vitamin D therapy, and was inversely associated with age, male sex, hemoglobin, dialysis dose, diabetes, HIV, and treatment in Japan. All-cause and cardiovascular mortality were associated with serum PTH concentration (Table 5). Not surprisingly, the risk of new PTX was also strongly predicted by the baseline PTH concentration (Table 5).

Vitamin D therapy

Overall, 52% of point-prevalent patients were treated with some form of vitamin D therapy (Table 6). The use of vitamin D therapy varied among facilities, ranging from 0% to 100%. At the 25th facility percentile, 37% of patients received vitamin D, compared to 67% of patients at the 75th facility percentile. Parenteral vitamin D therapy was largely restricted to U.S. facilities (44% in U.S., 4% in Europe, and <1% in Japan). Vitamin D therapy was given to 46% of patients with a low PTH concentration and to 65% of patients with a high PTH concentration (Table 7). After excluding patients whose serum phosphorus and calcium levels exceeded the guideline limit, vitamin D therapy was used in only 69% of patients with high PTH concentrations. Even when using less stringent PTH target values, vitamin D was used by 46% to 50% of patients with a PTH <100 pg/mL and by 66% to 74% of patients with a PTH concentration >400 pg/mL (Table 7). Future PTX was significantly less likely among patients who were receiving vitamin D therapy at baseline (OR 0.62, $P = 0.01$). Vitamin D therapy was not significantly associated with mortality.

Phosphorus binder therapy

Phosphorus binders were taken by 81% of the patient sample (Table 6). Use of phosphorus binders varied modestly by facility. The specific binding agents in use during the time of the study were calcium carbonate (53%), calcium acetate (26%), aluminum salts (6%), calcium citrate (1%), and magnesium salts (1.5%). Sevelamer was used by only 0.1% of patients, as it only became available at the end of the study observation period. Phosphorus binder therapy was administered to approximately 77% of patients with a low serum phosphorus concentration and to 83% of patients with a high serum phosphorus concentration (Table 7). The same percentage of patients (83%) received phosphorus binders whether

Table 7. Use of specific therapies by laboratory guideline range (initial cross-section)

	Guideline range (% of patients)					
	Below	Within	Above	Below	Within	Above
Serum PTH	<150 ($N = 2677$)	150–300 ($N = 1164$)	>300 ($N = 1399$)	<100 ($N = 2018$)	100–400 ($N = 2222$)	>400 ($N = 1000$)
Patients receiving vitamin D preparation	46.1	53.1	65.7	46.0	53.4	65.7
Patients with Ca <9.5 and P <5.5 receiving vitamin D preparation	47.2	53.8	69.1	49.5	51.1	73.5
Serum phosphorus	<3.5 ($N = 621$)	3.5–5.5 ($N = 3340$)	>5.5 ($N = 4221$)	<3.0 ($N = 321$)	3.0–6.0 ($N = 4618$)	>6.0 ($N = 3243$)
Patients receiving phosphorus binder therapy	76.8	83.3	83.4	75.1	82.7	83.9
Albumin-corrected calcium	<8.4 ($N = 644$)	8.4–9.5 ($N = 2792$)	>9.5 ($N = 3462$)	<7.9 ($N = 243$)	7.9–10.0 ($N = 4647$)	>10.0 ($N = 2008$)
Patients with dialysate Ca ≤2.5	38.2	44.1	46.5	39.5	44.0	47.2

Initial cross-section taken at study start (1996 in the US, 1998 in Europe, 1999 in Japan).

serum phosphorus was high or within range. Also, similar percentages of patients were potentially overusing or underusing phosphorus binders when the analysis was conducted using less stringent threshold concentrations (<3.0 mg/dL, >6.0 mg/dL).

Dialysate calcium concentration

The K/DOQI guidelines recommend a dialysate concentration of 2.5 mEq/L, while the EBPG does not make a specific recommendation. The average dialysate calcium concentration was 2.9 mEq/L, with almost 60% of patients exceeding the K/DOQI recommendation (Table 6). The recommended low calcium dialysate was employed more often in U.S. facilities than in Europe and Japan. Table 7 shows that a low dialysate calcium concentration (≤2.5 mEq/L) was used for 38% of patients with a low serum calcium concentration (<8.4 mg/dL) and for 47% of patients with a high serum calcium concentration (>9.5 mg/dL). Similar use patterns were seen for patients at more extreme cut-points of serum calcium. All-cause (but not cardiovascular) mortality risk was significantly associated with higher dialysate calcium concentration, adjusted for the serum concentrations of calcium and phosphorus (Table 5). The risk of PTX was inversely associated with the dialysate calcium concentration.

DISCUSSION

The topic of mineral metabolism in renal failure has traditionally focused on bone health [1]. However, there is growing evidence that factors involved in mineral metabolism are associated with other disease processes. Specifically, a strong association between mortality and markers of mineral metabolism has been reported in several observational studies [7, 8]. Altered levels of serum calcium, phosphorus, and calcium-phosphorus product influence the occurrence and rate of soft tissue and, particularly, vascular calcification (mineralization) [9, 10]. Vascular mineralization probably contributes to vascular occlusive disease, including the coronary, peripheral, and cerebral circulations [11]. These findings reveal the potential for optimal mineral metabolism management to advance both bone and vascular health of dialysis patients [12]. Guidelines have recently been promulgated [5, 6] based on the reported association of cardiovascular [13, 14] and skeletal consequences of altered mineral metabolism.

The present study provides a useful measure of how closely the new EBPG and K/DOQI mineral metabolism guidelines were met during 1996 to 2001, prior to publication of the guidelines in 2002 and 2003. The study provides a benchmark for evaluating practice improvements following dissemination of the new guidelines. The DOPPS is particularly well suited to analyze guideline compliance because it involves representative samples of hemodialysis facilities and patients from 7 countries with large populations of hemodialysis patients. The characteristics of DOPPS patients closely match other source reports from these same countries (Table 1) [15]. Furthermore, this study adds to the body of observational evidence concerning the relationship between patient survival and mineral metabolism indicators and practices. PTX was also studied as an outcome measure of an extreme and potentially avoidable means of managing abnormal mineral metabolism.

Most patients studied in the 1996 to 1999 initial cross-section fell outside of the recommended guideline values for phosphorus, calcium, and PTH, and nearly 44% of patients exceeded the recommended upper range for calcium-phosphorus product (Table 3). These findings reveal clear opportunities for improvement in patient care and potentially improved outcomes.

This study also expands our understanding of the relationship between altered mineral metabolism and outcomes. As noted in other studies, high levels of serum calcium, serum phosphorus [8], calcium-phosphorus product [8], and PTH are associated with increased patient mortality (Table 5, Figs. 1 to 3). Our results generally affirm the EBPG and K/DOQI guideline limits for these

lab values. In addition, these factors are also associated with a higher risk of subsequent PTX (Table 5). Cardiovascular mortality risk tended to be larger than all-cause mortality risk, consistent with a potential pathogenic pathway involving vascular mineral deposition. We found increased mortality at lower concentrations of phosphorus (Fig. 1), perhaps due to nutritional deficiency that was not adjusted for in the statistical models. We also found decreased mortality at lower concentrations of serum calcium (Fig. 2), in apparent contrast to at least one prior study showing increased mortality [16]. Broader adjustment for serum phosphorus, PTH, comorbidities, and use of albumin-corrected calcium (recommended by K/DOQI and EBPG) may explain this difference.

Parathyroid hormone plays a central role in mineral metabolism, especially bone health. High- and low-turnover bone disease have been attributed to high and low PTH concentrations, respectively [1]. Despite the traditional focus on hyperparathyroidism in renal failure, it is noteworthy that low PTH concentrations were reported for the majority of hemodialysis patients in this study (Table 3). PTH concentrations below and above the K/DOQI guideline levels were significantly associated with age, gender, race, duration of ESRD, and several comorbid conditions (Table 4). Our study agrees with others in finding that black patients were more likely to have high PTH levels and less likely to have low PTH levels [17, 18]. The association with ESRD duration is a probable consequence of chronic parathyroid gland stimulation and hyperplasia. A PTH concentration below the guideline limit was directly associated with the dialysate calcium concentration, suggesting oversuppression of PTH that could be modified by choice of dialysate composition. Similarly, PTH concentration above the guideline limit was inversely associated (approaching significance at $P = 0.053$) with the dialysate calcium concentration, suggesting a potentially modifiable practice that results in excessive PTH stimulation. In contrast, low and high PTH were negatively and positively associated, respectively, with vitamin D therapy, suggesting the general appropriateness of prescribing vitamin D in response to PTH level.

PTX is one therapeutic option for management of advanced hyperparathyroidism. We found large variation among countries in the use of this operation, both at baseline and during the course of the study (Table 2). Although PTX was too infrequent to characterize as a facility practice pattern, the large variation across countries suggests inconsistent indications and thresholds for parathyroid surgery. Variability of this magnitude argues for best-practice guidelines and clinical trials. Notwithstanding large variability in the use of the procedure, the risk of PTX was strongly associated with baseline laboratory values, including concentrations of serum phosphorus, calcium, and PTH (Table 5).

Several other treatments are available to manage mineral metabolism in dialysis patients, including vitamin D analogs and phosphorus binders. The use of vitamin D showed large variation across facilities (67% of patients at the 75th facility percentile vs. 37% at the 25th facility percentile) and countries (Table 6). The use of parenteral vitamin D preparations was mainly restricted to the U.S., probably due to Medicare reimbursement policies that only cover injectable medications. Considerably less variability was seen in the use of phosphorus binders across facilities (93% of patients at the 75th facility percentile vs. 77% at the 25th facility percentile) and countries (Table 6).

Overall, we found suggestive evidence for inappropriate use of vitamin D and phosphorus binder therapy (Table 7). Specifically, almost half the patients with low PTH were receiving vitamin D, despite apparent oversuppression by current standards. In contrast, less than two thirds of patients with high PTH received vitamin D therapy. Vitamin D was also underused among patients with high PTH who had their serum calcium and phosphorus concentrations within the target range. In other words, hyperparathyroidism was untreated in over 30% of patients who lacked an apparent contraindication to vitamin D therapy. Conclusions about the appropriateness of vitamin D therapy may be questionable for patients with PTH values that are only slightly outside the target range. However, we found relatively high vitamin D use even among patients with a PTH concentration <100 pg/mL, and relatively low use among patients with a PTH concentration above 400 pg/mL (Table 7). In a similar fashion, the study reveals a potential pattern of overuse of phosphorus binders among patients with low serum phosphorus concentration of less than 3.5 mg/dL (77% were treated), and underuse of phosphorus binders among patients with serum phosphorus concentration above 5.5 mg/dL (almost 17% were untreated). These estimates may overstate the problems somewhat, as they are based on single laboratory values and physicians may be adjusting therapy according to the results. However, it is notable that the use of phosphorus binders was very similar at less stringent levels of serum phosphorus (<3.0 mg/dL and >6.0 mg/dL, Table 7).

The dialysate calcium concentration varied by continent (Table 6). Overall, only 47% of patients with a high serum concentration of calcium were dialyzed with a low calcium bath (Table 7), indicating large opportunities for improved management of the serum calcium concentration. Dialysate calcium use was very similar for patients at more extreme levels of serum calcium (<7.9 mg/dL and >10.0 mg/dL, Table 7), arguing against overstated usage patterns due to patients who fell just slightly out of the target range. Mortality risk was significantly associated with the higher dialysate calcium concentration, independent of the effects of serum calcium and

phosphorus (Table 5). The mechanism for the independent association between mortality and dialysate calcium is not known, and the finding should be confirmed in other studies. In contrast to mortality, PTX risk was understandably lower in patients treated with higher concentrations of dialysate calcium (Table 5). We suggest that the potential mortality risk outweighs the PTX risk, supporting a general recommendation for use of low calcium dialysate. These findings come from a time when calcium salts constituted the major type of phosphorus binder, and before the availability of calcium- and aluminum-free binders.

Potential limitations of this observational study include inaccuracies in reporting. Data inaccuracies and noise usually lead to underestimation of associations, so that negative findings may be unreliable. However, it is worth noting that statistical stratification across DOPPS countries indicates that the observed associations are present in most countries.

CONCLUSION

The internationally representative DOPPS cohort reveals that laboratory values related to mineral metabolism fall outside the recommended range for the majority of hemodialysis patients. Mortality and PTX risks are strongly associated with altered mineral metabolism laboratory values. Improvements may be possible with modifications in the use of vitamin D preparations, phosphorus binders, and dialysate calcium concentrations.

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