Calcium, Phosphate, and Parathyroid Hormone Levels in Combination and as a Function of Dialysis Duration Predict Mortality: Evidence for the Complexity of the Association between Mineral Metabolism and Outcomes

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Abstract. Current literature suggests associations between abnormal mineral metabolism (MM) to cardiovascular disease in dialysis populations, with conflicting results. MM physiology is complex; therefore, it was hypothesized that constellations of MM parameters, reflecting this complexity, would be predictive of mortality and that this effect would be modified by dialysis duration (DD). Prevalent dialysis patients in British Columbia, Canada, who had measurements of calcium (Ca), phosphate (Pi), and parathyroid hormone (iPTH) between January and March 2000 were followed prospectively until December 2002. Statistical analysis included Cox proportional hazard models with Ca, Pi, and iPTH alone and in combination as explanatory variables; analyses were stratified by DD. The 515 patients included in this analysis represent British Columbia and Canadian dialysis populations: 69% were on hemodialysis, mean age was 60 ± 17 yr, 40% were female, and 34% had diabetes. Mean Ca and Pi values were 2.32 ± 0.22 mmol/L and 1.68 ± 0.59 mmol/L, respectively, and median iPTH was 15.8 pmol/L (25th to 75th percentile: 6.9 to 37.3 pmol/L). Serum Pi, after adjusting for demographic, dialysis type and adequacy, hemoglobin, and albumin, independently predicted mortality (risk ratio [RR], 1.56 per 1 mmol/L; 95% confidence interval [CI], 1.15 to 2.12; $P = 0.004$). When combinations of parameters were modeled (overall $P = 0.003$), the combinations of high serum Pi and Ca with high iPTH (RR, 3.71; 95% CI, 1.53 to 9.03; $P = 0.004$) and low iPTH (RR, 4.30; 95% CI, 2.01 to 9.22; $P < 0.001$) had highest risks for mortality as compared with the combination of high iPTH with normal serum Ca and Pi that had the lowest mortality and was used as index category. These effects varied across different strata of DD. This analysis demonstrates the importance of examining combinations of MM parameters as opposed to single variables alone and the effect of DD. In so doing, the complex interaction of time and MM can begin to be understand. Further exploration is required.

Recent investigations have implicated mineral metabolism (MM) as a risk factor for vascular calcification, cardiovascular disease (CVD), and mortality in patients who have kidney failure and are on dialysis. Studies have implicated elevated levels of serum phosphate (Pi), calcium-phosphate product (Ca-Pi), or intact parathyroid hormone (iPTH) (1–3) and others have implicated low iPTH levels (4, 5) in an association to mortality or CVD. Ongoing basic science and animal studies have linked abnormal MM to vascular calcification (6–9). Many of these studies have demonstrated abnormalities of vascular calcification in models of kidney disease specifically (10–18), thus suggesting a biologically plausible mechanism by which abnormal MM may have an impact on mortality, as has been seen in clinical studies. Nonetheless, conflicting results in clinical studies have led to confusion as to appropriate targets and therapeutic strategies.

It is well appreciated that MM physiology is complex and that its effects are dependent on interactions among the individual parameters themselves as well as to the surrounding environment (19). It is also recognized that abnormal bone metabolism develops in patients with end-stage kidney disease over time (19). The specific aspects of MM that place a patient at higher risk for adverse outcomes may be dependent on the interactions of this complex system and may evolve as patients progress along the continuum of chronic kidney disease. This has not been systematically studied to date.

To explore the complexity of the interactions of MM parameters, we undertook an analysis of a cohort of unselected

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prevalent dialysis patients in the province of British Columbia, Canada. We examined serum Ca, Pi, and iPTH levels alone and in combination as potential explanatory variables for survival, after adjusting for other variables known to be associated with survival in dialysis cohorts. This analysis describes how values of each MM parameter should be interpreted in the context of the other parameters and that time on dialysis modifies the relationship between MM and patient outcomes.

Materials and Methods

Study Population and Study Design

This cohort study was performed using data available from the British Columbia Renal Agency provincial database PROMIS (Patient Registration, Outcome and Management Information System). The data are collected prospectively in all chronic kidney disease and dialysis patients for clinical and administrative purposes, the former according to clinical protocols in each dialysis center. All patients who receive hemodialysis (HD) or peritoneal dialysis (PD) in British Columbia have signed informed consent disclosures at the initiation of dialysis allowing statistical and research analyses of their depersonalized data.

The study population included all prevalent dialysis patients in British Columbia who were alive and on dialysis as of January 2000 and who had measurements of serum Ca, serum Pi, and serum iPTH values entered into the database during the study entry period January to March 2000. The follow-up study period extended from Jan 2000 to December 2002. Patients with incomplete data sets relative to the purpose of current analysis were excluded. Comparisons of demographics and laboratory variables between those included and excluded in the analysis were performed. At the time of the study period, the only treatments in widespread use for disorders of mineral metabolism were Ca salts, aluminum binders, and oral vitamin D preparations

Predictors and Explanatory Variables

Demographic and clinical information included in the analysis was age, gender, date of first dialysis, diabetes status, previous transplant status, and dialysis type (PD or HD). Using date of first dialysis, the duration of dialysis (DD) was subsequently categorized into <6 mo, between 6 and 18 mo, and >18 mo, relative to study entry period.

Venous blood work drawn as part of regularly scheduled blood work was used for analysis. When more than one laboratory sample within the time frame included measurement of serum Ca or serum Pi, the samples that also included measurement of serum iPTH was used for analysis. Laboratory measurements of interest included hemoglobin, albumin (Alb), total serum Ca, serum Pi, iPTH, triglycerides, and total cholesterol, and all were measured using standard, provincially accredited laboratory techniques. Total serum Ca was corrected for level of serum Alb. Serum iPTH was measured by Immulite immunoassay for iPTH. All provincial laboratories were using the same assay at the time of study (normal range for iPTH, between 1.3 and 7.6 pmol/L).

Definitions and Parameters for Abnormal Mineral Metabolism

Serum Ca, serum Pi, Ca-Pi, and serum iPTH levels were used as the primary explanatory variables to determine the associations to patient outcomes, in both continuous and categorical forms. Each MM parameter was categorized according to whether it was at or above physiologic or current recommended target levels. The cutoff values above the target range for serum Ca, serum Pi, and Ca-Pi were clinically defined and based on published research. iPTH was categorized into tertiles on the basis of cohort-specific values, given the uncertainty about iPTH target ranges and the differences between assays used (20). All four variables were subsequently collapsed into dichotomous categories of higher and low/normal ranges for inclusion in the models. Specifically, serum Ca values were dichotomized as less than or greater than 2.50 mmol/L (10.0 mg/dl), serum Pi values were dichotomized as less than or greater than 1.78 mmol/L (5.5 mg/dl), Ca-Pi levels were dichotomized as less than or greater than 4.43 $mmol^2/L^2$ (<55 mg^2/dl^2), and iPTH was dichotomized as less than or greater than 27.3 pmol/L (273 pg/ml). Although this figure is higher than previously reported published results, it reflects the biologically pertinent cutoff for this cohort, obtained using the same methods as other published cutoffs. When using published cutoffs of >1.5 or two times the upper limit of normal (*i.e.*, for British Columbia values 7.6 pmol/L: 11.4 to 15.2), the impact of iPTH on patient outcomes of interest for this cohort was not consistent. Furthermore, given the controversies surrounding iPTH measurements and their interpretation and meaning in individuals and populations, we elected to use these population-specific tertiles of iPTH and then given the lack of difference between the two lower tertiles (<8.5 and 8.5 to 27.3) elected to collapse these into a dichotomous variable. Constellations of these dichotomized values for all three MM parameters (Ca, Pi, and iPTH) were constructed such that all possible combinations of the three parameters were included (eight categories).

Outcome Variables

The principle outcome for this analysis was mortality during the study follow-up period from January 2000 to December 2002. Mortality data were reported from each unit and validated using vital statistics reports from the province. Data were censored for transplantation and lost to follow-up for other reasons (*e.g.*, transferred to another province or country).

Statistical Analyses

Descriptive statistics are presented as mean with SD or median with interquartile range, depending on the underlying distribution. Continuous variables were compared using the *t* test or the Wilcoxon rank sum test, where appropriate. Categorical variables were compared using the χ^2 test. Patient survival was estimated using the Kaplan-Meier method. Survival curves, by combination of Ca, Pi, and iPTH levels, were compared using the log-rank test. $P < 0.05$ for two-sided univariate tests was considered significant.

The Cox proportional hazards model was used to identify important predictors of mortality. All models included the MM parameters as well as age, gender, diabetes, dialysis type, DD, hemoglobin, and albumin, factors shown to be predictive of mortality in dialysis patient cohorts.

A series of models were created to test our hypotheses. The initial model was based on inclusion of the adjusted MM parameters, with each parameter included as continuous variables. We tested interactions between MM parameters, and because they were statistically significant, we proceeded to construct a variable that captures eight possible combinations of three MM dichotomized parameters to improve interpretability of the results. The second model uses the constellation of MM parameters, with the combination that conveys the lowest rate of mortality as the reference category. We subsequently defined groups by DD at study entry (<6 mo, between 6 and 18 mo, >18 mo), after demonstrating statistically significant interactions with DD and based on our hypothesis that MM abnormalities need to be

evaluated in the context of exposure time. Statistical analyses were performing using the SAS software, version 8.2 (SAS Institute, Cary, NC).

Results

Baseline Clinical and Laboratory Characteristics

Of the total dialysis cohort, of HD and PD patients who were alive on January 1, 2000, 515 patients had complete data for the purpose of this analysis. There were neither demonstrable differences in demographics nor other available clinical or laboratory data when comparing patients with complete data sets *versus* those who did not have complete data sets for analysis.

Table 1 describes the entire cohort and demonstrates the similarities and differences between PD and HD patients. The overall cohort has a higher proportion of men (60%) and of HD patients (69%), in keeping with provincial statistics (21). At the study start, 125 patients had been on dialysis for <6 mo, 116 patients had been on dialysis for 6 to 18 mo, and 273 patients has been on dialysis for >18 mo. PD patients were younger, with a higher percentage of female and white patients, and had a shorter DD at study start than HD patients, as well as statistically significantly lower albumin and higher triglyceride levels than HD patients. Both HD and PD patients had evidence of optimal dialysis as measured conventionally by percent reduction urea and Kt/V, respectively, with >66% of both groups exceeding recommended high target levels.

The baseline MM parameters for the overall cohort, both continuous and categorical variables, and by dialysis type are also shown in Table 1. Of note, 61% and 81% of patients had serum Pi and Ca levels below or within target levels, respectively. Because there were no differences between serum values for Ca, Pi, and iPTH, we combined the cohort for further analyses while controlling for factors that were different in the pertinent analyses.

Figure 1 describes distribution of Ca, Pi, Ca*Pi product, and iPTH values at each of the different DD time points. Of note, the only statistically significant difference was demonstrable in serum Ca values, which were significantly higher in those with longer DD.

The majority of those who received vitamin D received an oral preparation of the drug at various intervals. There were significantly more patients on vitamin D analogues (85%) with iPTH >27.3 *versus* those with iPTH levels of <27.3 (62%; $P < 0.05$; data not shown). Within those category groups of iPTH, there was less vitamin D use when the serum Ca values were >2.5 mmol/L. Because vitamin D use is confounded by intention and issues of reverse causality, we did not include vitamin D in the models, but note here that the usage seems consistent with clinical practice and current guidelines, without an inordinate amount of vitamin D being used in those with lower iPTH levels.

The median follow-up after the study start in January 2000 was 31.6 mo (25th to 75th percentile, 14.7 to 36.0). During the follow-up period, there were 88 transplants, and nine patients moved out of the province.

Mortality: Impact of MM Parameters

Overall, 185 deaths occurred during the 3 yr of follow-up. Of 125 patients who had been on dialysis for <6 mo at study start, 39 (31%) died, 39 (33%) deaths occurred in 117 patients who had been on dialysis for between 6 and 18 mo, and 107 (39%) of 273 patients who had been on dialysis for >18 mo at study start died. One-year survival of patients who had been on dialysis for <6 mo at study start was 85.2%, patients who had been on dialysis for between 6 and 18 mo had 1-yr survival of 90.3%, and patients who had been on dialysis for >18 mo had 1-yr survival of 85.4% ($P = 0.49$).

Univariate Analysis. Table 2 describes univariate associations of the patient characteristics and mortality. The biochemical predictor variables are adjusted for age, gender, diabetes status, dialysis type, and DD. Note that in the univariate analysis, age, white race, diabetes, and low hemoglobin and albumin levels predict mortality. Of the MM parameters of interest, higher values of serum Pi and the highest categorical level of Ca-Pi product, as well as the constellation of the three parameters Ca, Pi, and iPTH, were statistically significant predictors of mortality.

Figure 2 displays survival as a function of iPTH, Ca, and Pi combinations. We presented unadjusted survival curves representing combinations that conveyed the highest and the lowest probability of survival, with all other combinations grouped into one curve.

Multivariate Analysis. Table 3 demonstrates the proportional hazards model created to describe the multivariate associations of MM parameters to mortality, which includes age, gender, race, diabetes, dialysis type, DD, adequacy of dialysis, hemoglobin, and albumin as well as all MM variables using continuous values, for the overall cohort. The Ca*Pi, Pi*iPTH, and Ca*Pi*iPTH interactions were statistically significant ($P = 0.003$, $P = 0.013$, and $P = 0.020$, respectively). Given the limited interpretability of these analyses, particularly with respect to MM variables, we analyzed the various clinically meaningful constellations of Ca, Pi, and iPTH.

Table 4 describes the proportional hazards model using all of the key variables described in Table 3 as having an impact on mortality, including DD, and each of the combinations of MM. The overall *P* value for all eight categories as a single variable is 0.003.

Given the statistically significant interaction of DD and combined MM parameters ($P = 0.0361$), we explored this interaction further as demonstrated in Table 5. Note the differential impact of the parameters and of various MM constellations depending on DD. The reference of higher iPTH and normal values of Ca and Pi were used as the index ratio of 1.

Irrespective of DD, age and albumin remain significant predictors of outcome. However, diabetes seems to be an important independent predictor only in those who survive >18 mo. Those who have been on dialysis for <6 mo seem to have a worse outcome when their Pi is elevated, irrespective of whether the Ca and iPTH are elevated or depressed, with the highest risk being identified in those with low iPTH, high Ca, and high Pi (risk ratio, 12.43; $P = 0.012$). In those who had been on dialysis for 6 to 18 mo before study start, there were

Table 1. Clinical characteristics of hemodialysis, peritoneal dialysis, and total patient cohorts[a]

	Total Patient Cohort	Hemodialysis Patients	Peritoneal Dialysis Patients	*P* Value
N	515	357 (69.3%)	158 (30.7%)	
Age	59.9 (±16.7)	60.8 (16.7)	57.7 (16.1)	0.051
Female gender	207 (40.2%)	133 (37.3%)	74 (46.8%)	0.041
Diabetes	176 (34.2%)	121 (33.9%)	55 (34.8%)	0.840
Race				0.005
White	298 (57.9%)	195 (54.6%)	103 (65.2%)	
Asian	141 (27.4%)	113 (31.6%)	28 (17.7%)	
other	76 (14.8%)	49 (13.7%)	27 (17.1%)	
Dialysis duration (mo)	20.1 (6.1–36.0)	24.3 (7.6–42.3)	12.4 (4.7–24.8)	<0.001
<6 mo	125 (24.3%)	78 (21.8%)	47 (29.7%)	0.001
6–18 mo	117 (22.7%)	67 (18.8%)	50 (31.6%)	
>18 mo	273 (53.0%)	212 (59.4%)	61 (38.6%)	
PRU	NA	72.99 (7.95)	NA	
Total Kt/V	NA	NA	2.40 (0.59)	
Dialysis adequacy				0.973
PRU ≤65, Kt/V ≤1.8	69 (13.4%)	47 (13.2%)	22 (13.9%)	
PRU 66–70, Kt/V 1.9–2.1	102 (19.8%)	71 (19.9%)	31 (19.6%)	
PRU >70, Kt/V >2.1	344 (66.8%)	239 (66.9%)	105 (66.5%)	
Previous transplant	36 (7.0%)	29 (8.1%)	7 (4.4%)	0.130
Hemoglobin (g/L)	115.5 (17.1)	114.6 (16.9)	117.3 (17.4)	0.102
Albumin (g/L)	35.0 (4.8)	35.6 (4.3)	33.5 (5.5)	<0.001
Cholesterol (mmol/L)	4.98 (1.15)	4.74 (1.34)	5.07 (1.06)	0.105
Triglycerides (mmol/L)	2.14 (2.13)	1.85 (1.17)	2.27 (1.54)	0.042
Ca (mmol/L)	2.32 (0.22)	2.32 (0.22)	2.31 (0.23)	0.694
< 2.50	416 (80.8%)	287 (80.4%)	129 (81.6%)	0.943
2.50–2.55	29 (5.6%)	21 (5.9%)	8 (5.1%)	
2.55–2.65	37 (7.2%)	25 (7.0%)	12 (7.6%)	
>2.65	33 (6.4%)	24 (6.7%)	9 (5.7%)	
Pi (mmol/L)	1.68 (0.53)	1.69 (0.56)	1.67 (0.46)	0.632
<1.78	315 (61.2%)	219 (61.3%)	96 (60.8%)	0.387
1.78–1.94	50 (9.7%)	30 (8.4%)	20 (12.7%)	
1.95–2.26	86 (16.7%)	60 (16.8%)	26 (16.5%)	
>2.26	64 (12.4%)	48 (13.4%)	16 (10.1%)	
Ca*Pi product ($mmol^2/L^2$)	3.90 (1.29)	3.91 (1.32)	3.87 (1.24)	0.771
<4.43	362 (70.3%)	249 (69.8%)	113 (71.6%)	0.552
4.43–4.84	51 (9.9%)	39 (10.9%)	12 (7.6%)	
4.84–5.64	59 (11.5%)	38 (10.6%)	21 (13.3%)	
>5.64	43 (8.4%)	31 (8.7%)	12 (7.6%)	
iPTH (pmol/L)	15.8 (6.9–37.3)	14.4 (6.5–36.3)	18.2 (8.2–39.1)	0.098
<27.3	343 (66.6%)	246 (68.9%)	97 (61.4%)	0.095
≥27.3	172 (33.4%)	111 (31.1%)	61 (38.6%)	
Pi, Ca, and iPTH				0.232
Pi <1.78, Ca <2.5, iPTH >27.3	80 (15.5%)	53 (14.8%)	27 (17.1%)	
Pi <1.78, Ca >2.5, iPTH >27.3	7 (1.4%)	4 (1.1%)	3 (1.9%)	
Pi <1.78, Ca >2.5, iPTH <27.3	49 (9.5%)	40 (11.2%)	9 (5.7%)	
Pi <1.78, Ca <2.5, iPTH <27.3	179 (34.8%)	122 (34.2%)	57 (36.1%)	
Pi >1.78, Ca <2.5, iPTH <27.3	87 (16.9%)	67 (18.8%)	20 (12.7%)	
Pi >1.78, Ca <2.5, iPTH >27.3	70 (13.6%)	45 (12.6%)	25 (15.8%)	
Pi >1.78, Ca >2.5, iPTH >27.3	15 (2.9%)	9 (2.5%)	6 (3.8%)	
Pi >1.78, Ca >2.5, iPTH <27.3	28 (5.4%)	17 (4.8%)	11 (7.0%)	

[a] PRU, percent reduction urea; Ca, calcium; Pi, phosphate; iPTH, parathyroid hormone

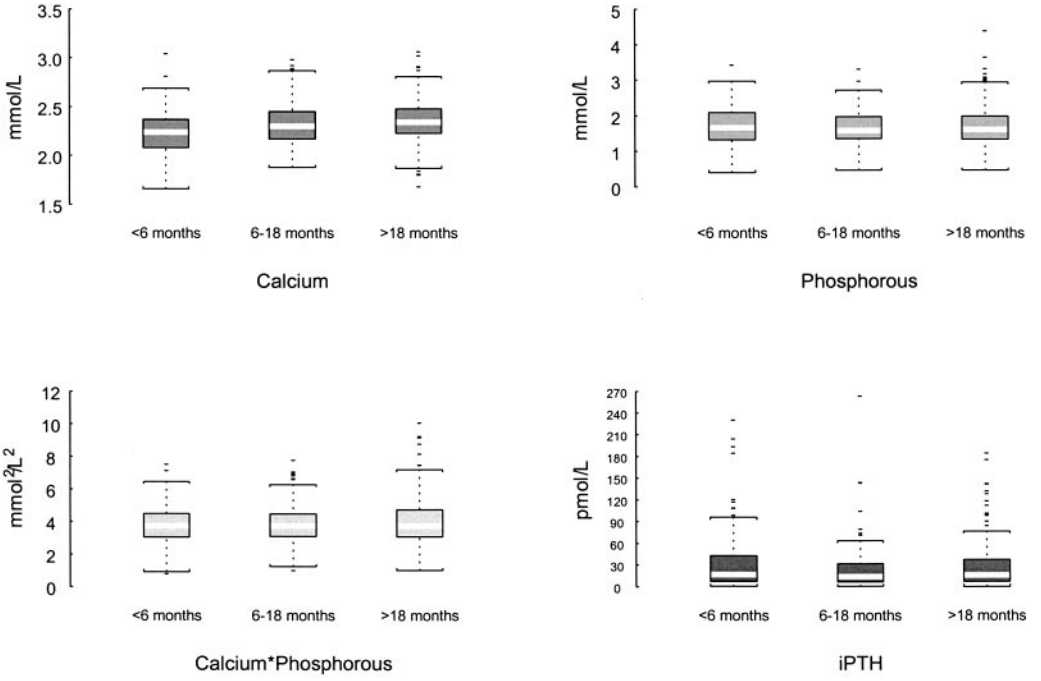

Figure 1. Distribution of parameters by dialysis duration for each of calcium (Ca), phosphate (Pi), Ca-Pi product, and parathyroid hormone (iPTH).

no specific constellations associated with an increase in mortality. It is interesting that those who were on dialysis >18 mo at the time of study start demonstrated differential risks of the different constellations of MM, with the highest risk ratios demonstrated in those constellations in which serum Ca was elevated.

Discussion

This analysis of a cohort of unselected prevalent dialysis patients demonstrates that specific constellations of serum iPTH, Ca, and Pi predict mortality and that those constellations of importance are modified by DD. The modeling performed in this analysis was an attempt to capture the complexity of the MM pathophysiologic system and to synthesize the disparate results from previous work that examined the associations of MM parameters to outcomes (1–4, 22). These findings may be helpful in defining both targets and inception cohorts in ongoing studies of the relationship of MM abnormalities, vascular calcification, and CVD outcomes in dialysis populations.

The univariate analysis and the results of the first model showed that serum Pi is a predictor of mortality when examined independently from the other MM parameters. This corroborates the findings of other studies (1, 2) but does not help to establish target Pi levels in patients at initiation of dialysis or at earlier time points. Furthermore, establishing target levels of Pi without knowledge of iPTH values may be problematic, as demonstrated within the context of our subsequent analysis.

We attempted to describe the complexity of the MM system using different constellations of MM parameters, using both current guidelines and our own cohort data analyzed to develop the constellations. The data are consistent with our hypotheses as to the relationship between abnormal MM system bone integrity and outcomes. The data demonstrate that the constellation of variables typically thought to describe "low bone turnover states," *i.e.*, low iPTH with high Ca and Pi values, is indeed associated with higher mortality. Note that given the ongoing controversies regarding target iPTH levels, assays used, and interpretation of normal and abnormal values, we used our cohort-specific cutoffs, which are approximately four times the upper limit of normal for our specific laboratory assay. The important issue here is not the actual level but the interpretation of the iPTH level relative to the other mineral metabolism values. Stratification for DD shows that evidence of high Pi with low iPTH and high Ca is an independent predictor of mortality in patients who have been on dialysis for <6 mo. Different constellations seem to confer differ risks for mortality after controlling for other variables known to have an impact on patient outcomes.

Stratification for DD provides insight into the apparent discordance of previous investigations. Studies have demonstrated that those with lowest iPTH levels at dialysis start are more likely do to die (4, 5), and others have demonstrated the adverse impact of high serum iPTH levels (1, 2, 23). Our data confirm that both are correct but that it is important to interpret levels of iPTH within the context of DD and levels of Ca and Pi. Prevalent dialysis patients have particular qualities that have allowed them to survive. Conversely, patients who die shortly after initiation of dialysis are inherently different from those who survive; they may have higher degrees of inflammation and malnutrition and therefore different risk profiles. Analysis of the entire cohort may have led to misleading results, with subsequent impact on target level setting of specific parameters. Similar issues are relevant to the discussion of the association of body mass index, cholesterol, and BP to adverse outcomes in ESRD and other chronic disease cohorts (24). Consideration of DD therefore is of particular importance

Table 2. Relative risk of mortality[a]

Variable	Alive (n = 330)	Decreased (n = 185)	Risk Ratio	(95% CI)	P Value
Age (*per 10 yr*)	55.1 (16.8)	68.4 (12.7)	1.48	1.33–1.65	<0.001
Gender (*female versus male*)	129 (39.1%)	78 (42.2%)	1.09	0.82–1.47	0.543
Diabetes	99 (30.0%)	77 (41.6%)	1.55	1.16–2.08	0.003
Race					0.028
White	180 (54.5%)	118 (63.8%)	1.00		
Asian	97 (29.4%)	44 (23.8%)	0.68	0.48–0.96	0.028
other	53 (16.1%)	23 (12.4%)	0.64	0.41–1.00	0.051
Dialysis type (*PD versus HD*)	101 (30.6%)	57 (30.8%)	1.08	0.79–1.49	0.613
Dialysis duration (*mo*)	18.6 (5.8–34.8)	24.2 (8.5–44.2)	1.00	0.99–1.01	0.111
<6 mo	86 (26.1%)	39 (21.1%)	1.00		
6–18 mo	78 (23.6%)	39 (21.1%)	0.95	0.61–1.48	0.814
>18 mo	166 (50.3%)	107 (57.8%)	1.16	0.80–1.67	0.437
Dialysis adequacy					0.070
PRU ≤65, Kt/V ≤1.8	40 (12.1%)	29 (15.7%)	1.00		
PRU 66–70, Kt/V 1.9–2.1	58 (17.6%)	44 (23.8%)	0.76	0.50–1.14	0.179
PRU >70, Kt/V >2.1	232 (70.3%)	112 (60.5%)	1.11	0.69–1.77	0.670
Previous transplant	26 (7.9%)	10 (5.4%)	0.71	0.38–1.35	0.298
Hemoglobin (per 5 g/L)[b]	116.7 (16.3)	113.2 (18.3)	0.93	0.89–0.97	<0.001
Albumin (g/L)[b]	36.0 (4.5)	33.3 (4.8)	0.91	0.88–0.94	<0.001
Cholesterol (mmol/L)[b]	4.98 (1.14)	4.98 (1.19)	0.99	0.77–1.29	0.988
Triglycerides (mmol/L)[b]	2.16 (1.56)	2.10 (1.17)	1.01	0.83–1.23	0.912
C (mmol/L)[b]					
continuous (per 1 mmol/L)	2.33 (0.21)	2.30 (0.25)	0.58	0.28–1.20	0.142
categorical					0.730
<2.50	269 (81.5%)	147 (79.5%)	1.00		
2.50–2.55	18 (5.5%)	11 (5.9%)	1.15	0.62–2.13	0.666
2.55–2.65	26 (7.9%)	11 (5.9%)	0.98	0.52–1.82	0.940
>2.65	17 (5.2%)	16 (8.6%)	1.33	0.79–2.25	0.287
Pi (mmol/L)[b]					
continuous (per 1 mmol/L)	1.70 (0.51)	1.65 (0.57)	1.37	1.02–1.85	0.041
categorical					0.025
<1.78	203 (61.5%)	112 (60.5%)	1.00		
1.78–1.94	33 (10.0%)	17 (9.2%)	1.32	0.79–2.22	0.293
1.95–2.26	55 (16.7%)	31 (16.8%)	1.53	1.02–2.30	0.039
>2.26	39 (11.8%)	25 (13.5%)	1.82	1.16–2.84	0.009
Ca*Pi product ($mmol^2/L^2$)[b]					
continuous (per 1 $mmol^2/L^2$)	3.95 (1.21)	3.81 (1.43)	1.12	0.99–1.26	0.081
categorical					0.033
<4.43	228 (69.1%)	134 (72.4%)	1.00		
4.43–4.84	39 (11.8%)	12 (6.5%)	0.76	0.42–1.39	0.382
4.84–5.64	37 (11.2%)	22 (11.9%)	1.45	0.92–2.29	0.108
>5.64	26 (7.9%)	17 (9.2%)	1.85	1.10–3.11	0.020
iPTH (pmol/L)[b]					
continuous (per 1 log iPTH)	15.9 (6.6–37.8)	15.7 (7.5–33.5)	0.99	0.88–1.11	0.870
categorical					
<27.3	216 (65.5%)	127 (68.6%)	1.21	0.88–1.66	0.232
≥27.3	114 (34.5%)	58 (31.3%)	1.00		
Pi, Ca, and iPTH*					0.042
Pi <1.78, Ca <2.5, iPTH>27.3	58 (17.6%)	22 (11.9%)	1.00		
Pi <1.78, Ca >2.5, iPTH>27.3	5 (1.5%)	2 (1.1%)	1.78	0.41–7.70	0.439
Pi <1.78, Ca >2.5, iPTH<27.3	31 (9.4%)	18 (9.7%)	1.51	0.80–2.85	0.200
Pi <1.78, Ca <2.5, iPTH<27.3	109 (33.0%)	70 (37.8%)	1.80	1.11–2.93	0.017
Pi >1.78, Ca <2.5, iPTH<27.3	59 (17.9%)	28 (15.1%)	2.16	1.21–3.85	0.008
Pi >1.78, Ca <2.5, iPTH>27.3	43 (13.0%)	27 (14.6%)	2.32	1.30–4.11	0.004
Pi >1.78, Ca >2.5, iPTH>27.3	8 (2.4%)	7 (3.8%)	2.75	1.15–6.54	0.023
Pi >1.78, Ca >2.5, iPTH<27.3	17 (5.2%)	11 (6.0%)	3.20	1.52–6.71	0.002

[a] CI, confidence interval; PD, peritoneal dialysis; HD, hemodialysis

[b] All biochemical characteristics' risk ratios were adjusted for age, gender, race, diabetes, and dialysis type and duration.

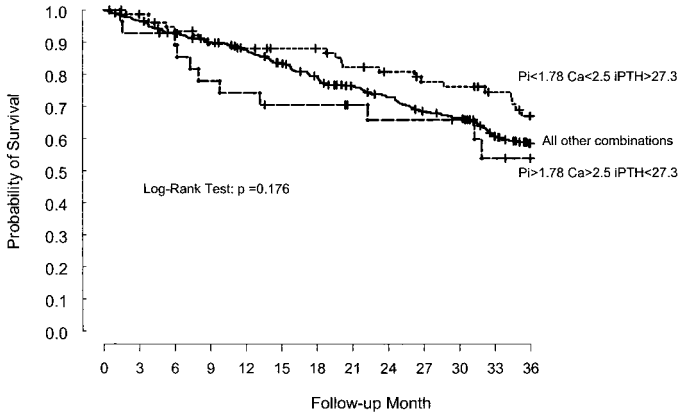

Figure 2. Kaplan-Meier survival curve, where survival is presented as a function of Ca, Pi, and iPTH combinations. Unadjusted survival curves representing the combinations that conveyed the highest and the lowest probability of survival in the overall group are presented and all other combinations grouped into one.

Table 3. Proportional hazards models of mortality using continuous values of biochemical parameters[a]

Variable	Overall	
	RR (95% CI)	*P* Value
Age (per 10 yr)	1.62 (1.43–1.83)	<0.001
Gender (female versus male)	1.19 (0.87–1.63)	0.283
Diabetes	1.84 (1.33–2.56)	<0.001
Dialysis type (PD versus HD)	1.21 (0.85–1.73)	0.296
Dialysis duration (per 1 mo)	1.01 (1.00–1.01)	0.007
Race		
White	1.00	
Asian	0.64 (0.40–1.01)	0.057
other	0.60 (0.42–0.87)	0.006
Dialysis adequacy		
PRU ≤65, Kt/V ≤1.8	1.00	
PRU 66–70, Kt/V 1.9–2.1	0.69 (0.44–1.08)	0.102
PRU >70, Kt/V >2.1	0.86 (0.53–1.40)	0.552
Hemoglobin (per 5 g/L)	0.97 (0.92–1.02)	0.194
Albumin (per 1 g/L)	0.92 (0.88–0.96)	<0.001
Ca (per 1 mmol/L)	1.35 (0.61–2.97)	0.459
Pi (per 1 mmol/L)	1.56 (1.15–2.12)	0.004
iPTH (per 1 log iPTH pmol/L)	1.02 (0.91–1.52)	0.715

[a] RR, risk ratio.

Table 4. Proportional hazards models of mortality using combined biochemical parameters

Variable	All Patients	
	RR (95% CI)	*P* Value
Age (per 10 yr)	1.64 (1.45–1.86)	<0.001
Gender (female versus male)	1.13 (0.83–1.55)	0.450
Diabetes	1.85 (1.32–2.58)	<0.001
Dialysis Type (PD versus HD)	1.26 (0.88–1.79)	0.210
Dialysis duration (per 1 mo)	1.01 (1.00–1.01)	0.014
Race		
White	1.00	
Asian	0.58 (0.40–0.80)	0.004
other	0.59 (0.37–0.95)	0.029
Dialysis adequacy		
PRU ≤65, Kt/V ≤1.8	1.00	
PRU 66–70, Kt/V 1.9–2.1	0.67 (0.43–1.07)	0.091
PRU >70, Kt/V >2.1	0.88 (0.54–1.44)	0.602
Hemoglobin (per 5 g/L)	0.96 (0.91–1.01)	0.097
Albumin (per 1 g/L)	0.92 (0.88–0.95)	<0.001
Pi, Ca, and iPTH		
Pi <1.78, Ca <2.5, iPTH >27.3	1.00	
Pi <1.78, Ca >2.5, iPTH >27.3	2.67 (0.61–11.76)	0.195
Pi <1.78, Ca >2.5, iPTH <27.3	2.08 (1.08–3.99)	0.029
Pi <1.78, Ca <2.5, iPTH <27.3	1.81 (1.10–2.97)	0.020
Pi >1.78, Ca <2.5, iPTH <27.3	2.60 (1.43–4.73)	0.002
Pi >1.78, Ca <2.5, iPTH >27.3	2.90 (1.59–5.28)	<0.001
Pi >1.78, Ca >2.5, iPTH >27.3	3.71 (1.53–9.03)	0.004
Pi >1.78, Ca >2.5, iPTH <27.3	4.30 (2.01–9.22)	<0.001

in MM, in which from both a physiologic and an epidemiologic point of view, incident and prevalent patients will have different risk profiles and therefore targets.

CVD is the most common cause of morbidity and mortality in patients on dialysis (25), and arterial stiffness is thought to be one of the contributory pathophysiologic processes (26, 27). Vascular calcification is also common in this population (28–30). MM abnormalities have been associated with vascular calcification (29, 31, 32), arterial stiffness (33, 34), and adverse clinical outcomes such as congestive heart failure and death (1–3). Thus, the link between CVD and MM may be mediated through development of vascular calcification and subsequent arterial stiffness. Lower values of iPTH are thought to indicate low bone turnover (adynamic bone disease). The current understanding of low bone turnover state is that the bone is unable to buffer excess dietary Pi and oral Ca salts used for Pi binding, allowing for Ca-Pi deposition in extraosseous tissue, including the vasculature (35, 36). However, it is possible that not all patients with low levels of iPTH truly have low bone turnover; therefore, our finding that it was patients with low iPTH in conjunction with elevated serum Ca and Pi levels who had the highest risk for mortality may suggest that this constellation is a better clinical marker for either low bone turnover or adverse outcomes than iPTH alone. Thus, these findings may provide further preliminary evidence for the connection between MM and CVD via vascular calcification. Our finding that the lowest risk ratios are associated with

Table 5. Proportional hazards models of mortality using combined biochemical parameters by dialysis duration category

Variable	<6 Months		6–18 Months		>18 Months	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Age (per 10 yr)	1.50 (1.13–1.99)	0.005	1.60 (1.12–2.30)	0.011	1.80 (1.52–2.13)	<0.001
Gender (female versus male)	1.26 (0.51–3.07)	0.619	1.74 (0.82–3.70)	0.151	0.99 (0.65–1.49)	0.952
Diabetes	0.83 (0.39–1.79)	0.638	1.67 (0.78–3.59)	0.189	2.63 (1.65–4.19)	<0.001
Dialysis type (PD versus HD)	1.56 (0.62–3.96)	0.346	1.61 (0.71–3.63)	0.252	1.25 (0.72–2.18)	0.431
Dialysis duration (per 1 mo)	1.10 (0.85–1.34)	0.574	0.98 (0.89–1.10)	0.658	1.01 (1.00–1.02)	0.008
Race						
White	1.00		1.00		1.00	
Asian	0.32 (0.09–1.09)	0.069	0.75 (0.34–1.66)	0.478	0.63 (0.40–1.03)	0.065
other	0.63 (0.21–1.95)	0.426	0.26 (0.08–0.84)	0.024	0.78 (0.41–1.48)	0.450
Dialysis adequacy						
PRU ≤65, Kt/V ≤1.8	1.00		1.00		1.00	
PRU 66–70, Kt/V 1.9–2.1	1.91 (0.59–6.19)	0.281	0.38 (0.13–1.10)	0.075	0.44 (0.22–0.85)	0.015
PRU >70, Kt/V >2.1	3.10 (0.89–10.82)	0.076	0.78 (0.24–1.54)	0.675)	0.58 (0.29–1.16)	0.127
Hemoglobin (per 5 g/L)	0.88 (0.78–0.99)	0.029	0.98 (0.89–1.01)	0.710	0.99 (0.92–1.06)	0.758
Albumin (per 1 g/L)	0.81 (0.73–0.89)	<0.001	0.86 (0.78–0.96)	0.009	0.94 (0.89–0.99)	0.015
Pi <1.78, Ca <2.5, iPTH >27.3	1.00		1.00		1.00	
Pi <1.78, Ca >2.5, iPTH >27.3	/	/	/	/	4.12 (0.88–19.24)	0.072
Pi <1.78, Ca >2.5, iPTH <27.3	1.47 (0.13–16.49)	0.753	1.96 (0.49–7.88)	0.341	1.84 (0.80–4.26)	0.152
Pi <1.78, Ca <2.5, iPTH <27.3	2.12 (0.54–8.26)	0.280	0.80 (0.23–2.72)	0.716	2.04 (1.07–3.88)	0.031
Pi >1.78, Ca <2.5, iPTH <27.3	2.69 (0.53–13.65)	0.231	2.89 (0.80–10.47)	0.105	2.74 (1.26–5.96)	0.011
Pi >1.78, Ca <2.5, iPTH >27.3	4.69 (1.16–18.95)	0.030	2.20 (0.48–10.15)	0.313	3.03 (1.36–6.74)	0.007
Pi >1.78, Ca >2.5, iPTH >27.3	/	/	1.47 (0.14–15.26)	0.748	4.03 (1.46–11.11)	0.007
Pi >1.78, Ca >2.5, iPTH <27.3	12.43 (1.74–89.03)	0.012	2.96 (0.69–12.75)	0.145	3.84 (1.31–11.27)	0.014

higher iPTH levels, particularly in conjunction with normal serum Ca and Pi levels, reinforces the importance of maintenance of some iPTH activity, reflecting active bone turnover and therefore the ability to buffer Ca salts in patients who receive dialysis therapy.

There are a number of strengths of this analysis. First, we explore physiologically plausible hypotheses in a cohort of contemporary, well-dialyzed patients with relatively long follow-up. Given that the analysis describes associations and not causation, we cannot confirm that abnormal bone metabolism in dialysis patients leads to deposition of extraosseous Ca and subsequent mortality. However, the observations do add to the current body of literature attempting to link the biologic and animal data describing the relationship between abnormal mineral metabolism and mortality and serve to remind clinicians of the complexity of MM.

Second, the strategy whereby we stratified the analysis by DD may help to address the survival bias noted to complicate the interpretation of other cross-sectional studies in this population (24). Our findings of differential results based on DD serve to reemphasize the importance of longitudinal studies and controlled trials that are better able to explore the dynamic nature of the disease.

The data are drawn from a clinical database, and the data collection is performed on a routine basis (*i.e.*, not for administrative or remunerative reasons or as a database from a clinical trial). Thus, this analysis reflects the current state of care of patients in British Columbia, using clinical information that is available to clinicians who care for those patients. As such, this relatively large unselected cohort of patients is representative of dialysis unit patient groups, including HD and PD patients, and findings may be generalizable to the larger dialysis community.

Limitations of this study include that it is a cohort study, not a randomized controlled trial. We therefore can demonstrate only association, which although is in keeping with biologic plausibility is not causality, and these analyses have yet to link convincingly biologic phenomenon with clinical care and outcomes (*i.e.*, MM abnormalities with vascular calcification, which leads to death). Furthermore, the data are collected in the pre- non-Ca non-aluminum phosphate binder era; thus, the impact of the use of these medications cannot be described. We do report vitamin D use but did not place it in the model given the difficulties in corroborating the prescribed *versus* the ingested dose and the problems of contamination/bias by intention (that could not be readily sorted out with this database analysis). We did not have measures of extraosseous calcification, and specific causes of death are not recorded. Nonetheless, as described herein, the information used in the analyses represents that set of clinical information that is readily available to clinicians who care for patients and thus forms the basis of day-to-day clinical decision making.

Last, current accepted iPTH cutoffs do not reliably distinguish patients who do or do not have metabolic bone disease. These specific cutoff values as representing high or low is relatively arbitrary, consistent with previously published literature, but the iPTH values for "high" and "low" are slightly higher than previously published reports in earlier eras. We addressed this by first describing the distribution, then selecting tertile-specific data, and also ensuring consistency with published literature (*i.e.*, two to three times the upper limit of normal). The iPTH assay has recently been shown to measure an iPTH fragment that itself may contribute to low bone turnover, making the interpretation of iPTH levels to signify a specific bone turnover state difficult (20, 37, 38), although the significance of this fragment is in question (39). This limitation is not specific to this study, as all studies performed to date have had to consider this assumption regarding iPTH levels and reinforces the difficulty of establishing absolute target levels for iPTH based on literature that used older assays. Importantly, the key finding in this analysis is the need to contextualize iPTH levels within individual patients on the basis of specific Ca and Pi values.

Conclusion

We demonstrate the importance of analysis of which attempts to combine known factors in understanding complex physiologic processes and also that DD is an important modifier in which to interpret abnormalities of Ca, Pi, and iPTH. Furthermore, we demonstrate that the integration of all three easily measured components of MM need to be considered in conjunction with other factors to understand best the high mortality rate on dialysis. This analysis cannot address the specific pathophysiologic processes that occur in uremia and does not provide the definitive link between vascular calcification and death, but it does raise awareness that complex conditions need to be assessed with complex analyses. Because vascular calcification is prevalent in dialysis populations, (22, 28, 40) we believe that data to support the association between Ca, Pi, and iPTH disturbances and mortality should be interpreted using more complex analyses, as demonstrated herein. Our findings do not contradict but rather add to previous observations, some of which have been conflicting. This analysis raises awareness that complex conditions need to be viewed in complex analyses to guide future basic and clinical research initiatives, clinical trials, and clinical guidelines.

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