Changes in Markers of Mineral and Bone Disorders and Mortality in Incident Hemodialysis Patients

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Key Words

Epidemiology · Disorders of calcium/phosphate metabolism · Parathyroid hormone · Alkaline phosphatase · Nutrition · Statistical methods

Abstract

Background: Abnormalities in mineral and bone disorder (MBD) markers are common in patients with chronic kidney disease. However, previous studies have not accounted for their changes over time, and it is unclear whether these changes are associated with survival. **Methods:** We examined the association of change in MBD markers (serum phosphorus (Phos), albumin-corrected calcium (Ca_{Alb}), intact parathyroid hormone (iPTH) and alkaline phosphatase (ALP)) during the first 6 months of hemodialysis (HD) with all-cause mortality across baseline MBD strata using survival models adjusted for clinical characteristics and laboratory measurements in 102,754 incident HD patients treated in a large dialysis organization between 2007 and 2011. **Results:** Across all MBD markers (Phos, Ca_{Alb}, iPTH and ALP), among patients whose baseline MBD levels were higher than the reference range, increase in MBD levels was associated with higher

mortality (reference group: MBD level within reference range at baseline and no change at 6 months follow-up). Conversely, decrease in Phos and iPTH, among baseline Phos and iPTH levels lower than the reference range, respectively, were associated with higher mortality. An increase in ALP was associated with higher mortality across baseline strata of ALP ≥ 80 U/l. However, patients with baseline ALP < 80 U/l trended towards a lower risk of mortality irrespective of the direction of change at 6 months follow-up. **Conclusions:** There is a differential association between changes in MBD markers with mortality across varying baseline levels in HD patients. Further study is needed to determine if consideration of both baseline and longitudinal changes in the management of MBD derangements improves outcomes in this population.

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Introduction

High serum concentrations of phosphorus (Phos), calcium, intact parathyroid hormone (iPTH) and alkaline phosphatase (ALP) are frequently found in patients with advanced chronic kidney disease (CKD) and are associ-

Fig. 1. Cohort construction.

ated with increased cardiovascular disease and mortality, especially in those with end-stage renal disease (ESRD) [1–9]. In addition, changes in these minerals may result in CKD-mineral and bone disease (CKD-MBD), leading to structural and functional abnormalities in the bone and cardiovascular system, as well as higher morbidity and mortality in ESRD patients [10].

Although clinical practice guidelines recommend that the therapeutic management of CKD-MBD should be based on the trends of these MBD markers instead of a singular laboratory result [11–13], few studies have evaluated the association between changes in MBD markers over time with outcomes, or how baseline levels modify these relationships [9, 14]. Furthermore, previous studies have examined study populations with heterogeneous dialysis vintage. Mortality is highest during the early period after hemodialysis (HD) initiation [14, 15], and thus the association of these changes with all-cause mortality may differ in long-term HD patients. Therefore, we sought to examine the association between changes in serum concentrations of albumin-corrected calcium (Ca_{Alb}), Phos, iPTH and ALP in the first 6 months after initiation of dialysis with all-cause mortality across varying baseline concentrations of these MBD markers in a large contemporary cohort of incident HD patients.

Methods

Study Population and Data Source

We examined data from patients who initiated treatment within a large dialysis organization (LDO) in the US between 2007 and 2011, with follow-up concluding on December 31, 2011 [16]. This

study was approved by the Institutional Review Committees of Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California, Irvine, and the DaVita Clinical Research. The need for written consent was waived due to the study's large sample size, patient anonymity and non-intrusive nature.

Patients treated for at least 60 consecutive days were considered to be on maintenance HD. Patient follow-up was divided into consecutive patient quarters, representing 91-day intervals from the start of dialysis treatment. The baseline quarter (Q1) for each patient was defined as the first 91-day interval in which the patient was treated with HD. Patients were censored at the time of renal transplantation, transfer to a different LDO facility or at the end of the study period. Patients were excluded from this study if they were treated with modalities other than in-center HD, were treated for less than 91 days (only had 1 quarter of follow-up) or had missing data for Phos, Ca_{Alb} , iPTH and ALP measurements at baseline and the following quarter.

Demographic and Clinical Measures

The final study population was composed of 102,754 incident HD patients (fig. 1). Data obtained on mortality and baseline demographics, including self-categorized race/ethnicity and primary insurance were acquired from the LDO's electronic records database. Intravenous medications were also obtained from the LDO's records and calculated as median dose per week.

The following 11 pre-existing comorbidities were obtained from ICD-9 codes from the LDO's electronic records database: (1) diabetes mellitus, (2) hypertension, (3) congestive heart failure, (4) atherosclerotic heart disease, (5) cerebrovascular disease, (6) other cardiovascular disease, (7) chronic obstructive pulmonary disease, (8) history of cancer, (9) HIV, (10) alcohol abuse and (11) substance abuse.

Laboratory Measures

Blood samples were drawn using standard techniques in all dialysis clinics and were transported to the LDO's central laboratory in Deland, Florida, within 24 h. All laboratory values, including serum measurements of Phos, Ca_{Alb} , iPTH and ALP, were mea-

sured on a monthly basis and by automated and standardized methods. All repeated laboratory measurements were averaged during each 91-day interval to minimize the effects of short-term variability. When serum albumin concentration was <4.0 g/dl, we calculated Ca_{Alb} as follows: $Ca_{Alb} = \text{serum calcium (mg/dl)} + 0.8 \times (4.0 - \text{serum albumin (g/dl)})$ [17]. Delivered dialysis dose was estimated by single-pooled Kt/V using the urea kinetic model.

We chose the first 6-month interval of HD treatment to assess changes in the baseline and follow-up levels of CKD-MBD markers because serum Phos and iPTH concentrations tends to be high prior to the initiation of maintenance dialysis treatment and then gradually decreases and stabilizes usually within the first 6 months of treatment. Changes in MBD markers were calculated by subtracting the mean concentrations during the first quarter (Q1) from the mean concentrations during the second quarter (Q2).

We divided each baseline concentration of Phos, Ca_{Alb} , iPTH and ALP into 4 groups (Phos <3.5, 3.5–<5.5, 5.5–<7.5 and ≥ 7.5 mg/dl; Ca_{Alb} <8.4, 8.4–<9.5, 9.5–<10.2 and ≥ 10.2 mg/dl; iPTH <150, 150–<300, 300–<600 and ≥ 600 pg/ml; ALP <80, 80–<120, 120–<160 and ≥ 160 U/l, respectively) based on prior studies [9, 18]. Within each baseline category of each CKD marker, we examined the change in marker level from Q1 to Q2 across 3 groups: unchanged, increased and decreased, based on the following intervals per marker: Phos: ± 0.5 mg/dl, Ca_{Alb} : ± 0.2 mg/dl, iPTH: ± 50 pg/ml and ALP: ± 10 U/l. For example, the change in Phos categories were ‘unchanged’ (± 0.5 mg/dl), ‘increased’ (> 0.5 mg/dl) and ‘decreased’ (< -0.5 mg/dl). These intervals were determined by the distribution of the change between quarters in the cohort. We categorized patients into a total of 12 groups according to baseline level and directionality of change (4-by-3) and examined their associations with all-cause mortality.

Statistical Methods

Data were summarized using proportions, means $\pm$ SD, medians (interquartile range (IQR)), where appropriate. Tests for trend analyses were used to quantify the relationship among baseline CKD-MBD marker groups.

Cox proportional hazards models were used to determine the relationship between change in blood concentrations of CKD-MBD-related parameters (Phos, Ca_{Alb} , iPTH and ALP) and all-cause mortality across baseline strata. Follow-up time started after 91 days from HD initiation. For each analysis, 3 levels of hierarchical adjustments were examined:

(I) Unadjusted models included entry calendar quarter.

(II) Case-mix adjusted models that included all variables included in the unadjusted model plus age, sex, race/ethnicity (White, African American, Hispanic, Asian and other), 11 pre-existing comorbidities as well as primary insurance (Medicare, Medicaid and other), vascular access (catheter, arteriovenous fistula or graft), cause of ESRD (diabetes, hypertension, glomerulonephritis, cystic kidney disease, other) and dialysis dose as indicated by single-pool Kt/V (spKt/V). Both baseline and subsequent quarter values of vascular access and spKt/V were included in the model.

(III) Models adjusted for case-mix and malnutrition-inflammation complex syndrome (MICS) covariates, which included all of the covariates in the case-mix model as well as the following quarterly averaged variables: body mass index and laboratory surrogates associated with clinical outcomes in HD patients including serum concentrations of (1) albumin, (2) creatinine, (3) total iron

binding capacity, (4) ferritin, (5) bicarbonate, (6) peripheral white blood cell count, (7) lymphocyte percentage, (8) hemoglobin, (9) iron saturation, (10) normalized protein catabolic rate. Models were additionally adjusted for Phos, Ca_{Alb} , iPTH and ALP, unless the particular CKD-MBD marker was the exposure of interest. Finally, the median dose per week of active vitamin D medications administered intravenously was also included. Both baseline and subsequent quarter values were included for all laboratory covariates and medication dosages to account for the change in these variables over time.

For each MBD marker of interest, we examined the effect modification of the association between the change in MBD level with mortality according to baseline MBD level in the fully adjusted case-mix and MICS model. These interaction terms were evaluated by Wald tests simultaneously for each CKD-MBD-related parameters.

In each model, the referent group was the second lowest baseline concentration group and exhibited no change in the subsequent quarter (Phos 3.5–<5.5 mg/dl; Ca_{Alb} 8.4–<9.5 mg/dl; iPTH 150–<300 pg/ml; ALP 80–<120 U/l). In sensitivity analyses, the group exhibiting no change in concentration for each baseline strata was chosen as the referent group in order to compare the association of an excessive change in MBD marker concentration within each baseline strata.

Data was missing on average, 1% for the cohort. Missing values were handled by multiple imputation. All statistical analyses were carried out with SAS, version 9.4 (SAS Institute, Inc., Cary, N.C., USA).

Results

The final study population was composed of 102,754 incident HD patients with available measurements of Phos, Ca_{Alb} , iPTH and ALP during the first 6 months of treatment. Patients had a mean $\pm$ SD age of 63 ± 15 years, among whom 44% were female, 32% were African American and 60% were diabetic (table 1). In terms of comorbid conditions, 52% of patients had hypertension, 39% had a history of congestive heart failure and 15% had atherosclerotic heart disease prior to dialysis initiation. Overall follow-up time starting from 91 days after dialysis initiation was median (IQR): 475 (200–889) days.

Baseline serum concentrations of Phos, Ca_{Alb} , iPTH and ALP were median (IQR) 4.8 (4.2–5.6) mg/dl, 9.1 (8.8–9.4) mg/dl, 317 (201–490) pg/ml and 87 (69–114) U/l, respectively. Median changes in these concentrations from baseline to the subsequent quarter were 0.20 (–0.44 to 0.83) mg/dl, 0.04 (–0.20 to 0.30) mg/dl, –59.8 (–190.3 to 29.0) pg/ml and 0 (–12.5 to 12.7) U/l, respectively.

The association of the change in serum Phos, Ca_{Alb} , iPTH concentrations with all-cause mortality differed by baseline concentration (p interaction <0.001 for each MBD marker). There was also trend towards effect modification

Table 1. Demographic and clinical characteristics of 102,754 incident HD patient

Characteristics	n = 102,754	Characteristics	n = 102,754
Age, years	63±15	Congestive heart failure	39
Women, %	44	Atherosclerotic heart disease	15
Diabetes mellitus, %	60	Other cardiovascular disease	15
Median incident year	2009	Cerebrovascular disease	2
Race, %		COPD	5
White	46	History of cancer	2
African American	32	HIV	<1
Hispanic	15	Alcohol abuse	<1
Asian	3	Substance abuse	<1
Other	4	Serum levels	
Primary insurance, %		Albumin, g/dl	3.5±0.5
Medicare	54	Creatinine, mg/dl	5.9±2.4
Medicaid	7	TIBC, mg/dl	226.2±48.3
Other	39	CO ₂ , mEq/l	23.5±2.7
Access, %		Ferritin, ng/ml	276 (160–472)
Central venous catheter	77	White blood cell, ×10 ³ /mm ³	7.8±2.6
AV fistula	15	Iron saturation ratio, %	23.0±8.8
AV graft	4	Blood hemoglobin, g/dl	11.2±1.2
Unknown	3	Lymphocyte, %	20.8±7.4
ESRD reason, %		Phos, mg/dl	5.0±1.2
Diabetes	46	Ca _{Alb} , mg/dl	9.1±0.6
Hypertension	30	iPTH, pg/ml	317 (201–490)
GN	9	ALP, U/l	87 (69–114)
Cystic kidney disease	2	Intravenous medication	
Other	13	Active vitamin D user, %	64
spKt/V	1.5±0.3	Change in MBD levels	
KRU, ml/min	4.1±3.4	Phos, mg/dl	0.20 (–0.44 to 0.83)
Protein catabolic rate, g/kg/day	0.8±0.2	Ca _{Alb} , mg/dl	0.04 (–0.20 to 0.30)
Body mass index, kg/m ²	28±7	iPTH, pg/ml	–59.8 (–190.3 to 29.0)
Comorbidities, %		ALP, U/l	0 (–12.5 to 12.7)
Hypertension	52		

of the association of change in ALP concentrations and mortality according to baseline ALP level (*p* interaction = 0.054). Therefore, the following survival analyses were conducted after stratifying patients into 12 groups according to 4 baseline groups and 3 levels of change in the subsequent quarter.

Changes in Serum Phosphorous Concentrations and All-Cause Mortality

The median (IQR) baseline serum Phos concentration was 4.8 (4.2–5.6) mg/dl. Patients with higher baseline Phos concentrations were more likely to be younger, male, Hispanic, have a lower residual renal urea clearance (KRU) and have a history of congestive heart failure (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000444890).

Table 2 and figure 2 show the all-cause mortality hazard ratios (HRs) for 3 levels of change from baseline to the

next quarter across 4 groups of baseline serum Phos concentrations (reference: baseline serum Phos 3.5–<5.5 mg/dl and unchanged from Q1 to Q2). Among patients whose serum concentrations did not change from baseline to the subsequent quarter of treatment, baseline serum Phos concentrations showed a J-shaped association with mortality, with the highest baseline strata (Phos ≥7.5 mg/dl) exhibiting the highest mortality risk (aHR 2.01, 95% CI 1.72–2.36). Relative to the reference group, patients who experienced an increase or decrease in Phos in the subsequent quarter had a higher risk of mortality across all strata of baseline Phos ≥3.5 mg/dl.

Adjusted HR for all-cause mortality tended to be highest in patients who experienced a Phos increase >0.5 mg/dl in the subsequent quarter, especially among the highest baseline concentrations of Phos (Phos 5.5–<7.5 and ≥7.5 mg/dl). Similarly, an excessive fall of <–0.5 mg/dl from low baseline Phos concentrations of <3.5 mg/dl was also

Table 2. All-cause mortality HRs in baseline serum Phos groups and their changes in 102,754 incident HD patients

Baseline Phos group, mg/dl	Phos change, mg/dl	n	Event rate*	Unadjusted		Case-mix adjusted		Case-mix and MICS-adjusted	
				HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<3.5	Decreased (<-0.5)	305	607	4.01 (3.40–4.73)	<0.0001	3.11 (2.63–3.67)	<0.0001	1.67 (1.41–1.97)	<0.0001
	Unchanged (± 0.5)	2,583	277	1.80 (1.68–1.94)	<0.0001	1.49 (1.39–1.60)	<0.0001	1.08 (1.00–1.16)	0.0486
	Increased (>0.5)	5,088	233	1.51 (1.43–1.60)	<0.0001	1.31 (1.24–1.38)	<0.0001	1.05 (0.99–1.11)	0.1061
3.5–<5.5	Decreased (<-0.5)	11,335	199	1.29 (1.24–1.35)	<0.0001	1.23 (1.18–1.29)	<0.0001	1.12 (1.07–1.17)	<0.0001
	Unchanged (± 0.5)	28,840	154	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Increased (>0.5)	25,675	166	1.08 (1.04–1.11)	<0.0001	1.12 (1.08–1.16)	<0.0001	1.14 (1.10–1.18)	<0.0001
5.5–<7.5	Decreased (<-0.5)	10,251	143	0.92 (0.88–0.97)	0.0006	1.07 (1.02–1.12)	0.006	1.22 (1.16–1.28)	<0.0001
	Unchanged (± 0.5)	9,343	120	0.77 (0.74–0.81)	<0.0001	0.98 (0.93–1.03)	0.5016	1.23 (1.17–1.30)	<0.0001
	Increased (>0.5)	6,536	137	0.88 (0.84–0.93)	<0.0001	1.21 (1.14–1.28)	<0.0001	1.53 (1.44–1.62)	<0.0001
≥ 7.5	Decreased (<-0.5)	1,607	130	0.84 (0.76–0.93)	0.0007	1.21 (1.09–1.34)	0.0005	1.57 (1.41–1.75)	<0.0001
	Unchanged (± 0.5)	647	139	0.90 (0.77–1.04)	0.1597	1.33 (1.14–1.55)	0.0004	2.01 (1.72–2.36)	<0.0001
	Increased (>0.5)	544	156	1.01 (0.86–1.18)	0.9421	1.69 (1.44–2.00)	<0.0001	2.31 (1.95–2.73)	<0.0001

* Per 1,000 patient-years.

Fig. 2. Association of change in serum Phos and all-cause mortality across strata of baseline concentration (case-mix and MICS-adjusted).

Table 3. All-cause mortality HRs in baseline Ca_{Alb} groups and their changes in 102,754 incident HD patients

Baseline Ca _{Alb} group, mg/dl	Ca _{Alb} change, mg/dl	n	Event rate*	Unadjusted		Case-mix adjusted		Case-mix and MICS-adjusted	
				HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<8.4	Decreased (<-0.2)	737	156	0.99 (0.84–1.16)	0.9089	1.21 (1.03–1.42)	0.022	1.10 (0.94–1.30)	0.2373
	Unchanged (±0.2)	1,844	144	0.92 (0.83–1.02)	0.1032	1.03 (0.93–1.15)	0.5574	1.03 (0.93–1.15)	0.5680
	Increased (>0.2)	6,460	131	0.84 (0.79–0.89)	<0.0001	0.99 (0.93–1.05)	0.7055	1.03 (0.97–1.09)	0.3494
8.4–<9.5	Decreased (<-0.2)	14,425	156	0.99 (0.96–1.03)	0.7456	1.05 (1.01–1.09)	0.0131	1.05 (1.01–1.09)	0.0168
	Unchanged (±0.2)	32,946	156	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Increased (>0.2)	24,586	163	1.05 (1.01–1.08)	0.0071	1.09 (1.06–1.13)	<0.0001	1.07 (1.03–1.11)	0.0003
9.5–<10.2	Decreased (<-0.2)	8,612	158	1.02 (0.97–1.06)	0.4651	1.03 (0.98–1.07)	0.2593	1.02 (0.97–1.07)	0.3738
	Unchanged (±0.2)	7,498	179	1.16 (1.10–1.21)	<0.0001	1.12 (1.07–1.18)	<0.0001	1.07 (1.02–1.13)	0.0033
	Increased (>0.2)	3,006	218	1.41 (1.33–1.51)	<0.0001	1.39 (1.30–1.49)	<0.0001	1.16 (1.09–1.24)	<0.0001
≥10.2	Decreased (<-0.2)	1,844	194	1.25 (1.15–1.36)	<0.0001	1.17 (1.07–1.27)	0.0003	1.14 (1.05–1.24)	0.0017
	Unchanged (±0.2)	531	202	1.30 (1.12–1.51)	0.0004	1.31 (1.13–1.52)	0.0005	1.09 (0.94–1.27)	0.2548
	Increased (>0.2)	265	388	2.51 (2.11–3.00)	<0.0001	2.23 (1.87–2.67)	<0.0001	1.70 (1.42–2.03)	<0.0001

* Per 1,000 patient-years.

associated with higher risk of mortality (aHR 1.67, 95% CI 1.41–1.97; fig. 2). This was also evident in sensitivity analysis where marker change was evaluated independently in each baseline stratum. An increase in Phos for patients in baseline strata Phos 3.5–<5.5 and 5.5–<7.5 mg/dl, as well as a further decrease from baseline Phos <3.5 mg/dl exhibited higher mortality in comparison to patients whose Phos measurements baseline were unchanged (online suppl. fig. 1).

Changes in Albumin-Corrected Serum Calcium Concentrations and All-Cause Mortality

Median (IQR) baseline serum Ca_{Alb} concentration was 9.1 (8.8–9.4) mg/dl. Patients with high baseline Ca_{Alb} concentrations were more likely to be older, female, African American and hypertensive (online suppl. table 2).

Table 3 shows the all-cause mortality HRs for 3 levels of change from baseline to the subsequent quarter across 4 groups of baseline serum Ca_{Alb} concentrations (reference: baseline serum Ca_{Alb} 8.4–<9.5 mg/dl and unchanged from Q1 to Q2). In unadjusted models, patients in the lowest baseline Ca_{Alb} stratum and who had a subsequent increase Ca_{Alb} had the lowest mortality risk. However, this association was attenuated after fully adjusting for case-mix and MICS variables. Similar to trends seen with Phos, there was a trend toward higher risk of mortality among patients who experienced an increase in Ca_{Alb} in their subsequent quarter across all baseline groups of Ca_{Alb} ≥8.4 mg/dl (fig. 3). The highest

mortality was seen in patients who experienced a further increase in Ca_{Alb} from already high baseline Ca_{Alb} concentrations (aHR 1.70, 95% CI 1.42–2.03). This association was also evident when examining the association of change with respect to baseline strata (online suppl. fig. 2). Finally, patients in baseline strata Ca_{Alb} 8.4–<9.5 and ≥10.2 mg/dl and who experienced a decrease in Ca_{Alb} in the next quarter had a higher risk of mortality compared to the reference group (aHR 1.05, 95% CI 1.01–1.09, aHR 1.14, 95% CI 1.05–1.24, respectively; fig. 3).

Change in Serum iPTH Level and All-Cause Mortality

Median (IQR) baseline serum iPTH concentrations were 317 (201–490) pg/ml. Patients with high baseline iPTH concentrations were more likely to be younger, African American and hypertensive (online suppl. table 3).

Table 4 shows the all-cause mortality HRs for 3 levels of change from baseline to the next quarter across 4 groups of baseline serum iPTH concentrations (reference: baseline serum iPTH 150–<300 pg/ml and unchanged from Q1 to Q2). In the unadjusted model, higher baseline iPTH concentrations were associated with better survival, irrespective of the direction of change in the subsequent quarter. However, after further adjustment for laboratory markers this association reversed, especially among patients whose iPTH increased in the next quarter across baseline groups of iPTH ≥150 pg/ml. Patients whose lev-

Table 4. All-cause mortality HRs in baseline serum iPTH groups and their changes 102,754 incident HD patients

Baseline iPTH group, pg/ml	iPTH change, pg/ml	n	Event rate*	Unadjusted		Case-mix adjusted		Case-mix and MICS-adjusted	
				HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<150	Decreased (<-50)	1,419	290	1.68 (1.54–1.85)	<0.0001	1.52 (1.39–1.67)	<0.0001	1.16 (1.06–1.28)	0.0019
	Unchanged ($\pm$ 50)	8,434	238	1.38 (1.31–1.45)	<0.0001	1.27 (1.20–1.33)	<0.0001	1.06 (1.00–1.11)	0.0375
	Increased (>50)	5,428	184	1.06 (1.00–1.13)	0.053	1.05 (0.99–1.12)	0.1109	1.02 (0.96–1.08)	0.5653
150–<300	Decreased (<-50)	11,122	206	1.19 (1.14–1.25)	<0.0001	1.11 (1.06–1.16)	<0.0001	1.03 (0.98–1.08)	0.2097
	Unchanged ($\pm$ 50)	12,468	173	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Increased (>50)	8,986	161	0.93 (0.88–0.98)	0.0077	1.01 (0.95–1.06)	0.8418	1.07 (1.02–1.13)	0.0129
300–<600	Decreased (<-50)	26,788	142	0.82 (0.79–0.86)	<0.0001	0.92 (0.88–0.96)	<0.0001	0.98 (0.93–1.03)	0.3784
	Unchanged ($\pm$ 50)	6,261	137	0.79 (0.74–0.84)	<0.0001	0.94 (0.88–1.00)	0.0414	1.03 (0.97–1.10)	0.3578
	Increased (>50)	5,115	145	0.84 (0.78–0.90)	<0.0001	1.06 (0.99–1.14)	0.1099	1.15 (1.07–1.24)	0.0003
$\geq$ 600	Decreased (<-50)	14,605	122	0.71 (0.67–0.74)	<0.0001	0.91 (0.86–0.95)	0.0001	1.02 (0.95–1.11)	0.5437
	Unchanged ($\pm$ 50)	806	132	0.77 (0.65–0.90)	0.0013	1.05 (0.89–1.24)	0.5417	1.15 (0.97–1.37)	0.1076
	Increased (>50)	1,324	153	0.89 (0.79–1.00)	0.0448	1.20 (1.07–1.36)	0.0025	1.26 (1.09–1.47)	0.0019

* Per 1,000 patient-years.

Fig. 3. Association of change in serum Ca_{Alb} and all-cause mortality across strata of baseline concentration (case-mix and MICS-adjusted).

Fig. 4. Association of change in serum iPTH and all-cause mortality across strata of baseline concentration (case-mix and MICS-adjusted).

els of iPTH had increased over time from baseline iPTH ≥ 600 pg/ml experienced the highest risk of mortality (aHR 1.26, 95% CI 1.09–1.47). Among patients whose iPTH concentrations had decreased in the subsequent quarter, only patients whose baseline iPTH was <150 pg/ml experienced a higher risk of mortality (aHR 1.16, 95% CI 1.06–1.28; fig. 4). In sensitivity analysis, patients whose iPTH levels increased from baseline iPTH of 150– <300 and 300– <600 pg/ml were also at a higher risk of mortality. However patients with a baseline iPTH of 300– <600 pg/ml were at a modest but significantly lower risk of mortality when iPTH decreased in the next quarter in comparison to patients who did not experience a change (online suppl. fig. 3).

Change in Serum ALP Level and All-Cause Mortality

Median (IQR) baseline serum ALP concentrations were 87 (69–114) U/l. Patients with high baseline ALP concentrations were more likely to be younger, female,

diabetic, and have history of other cardiovascular disease (online suppl. table 4).

Table 5 shows the all-cause mortality HRs for 3 levels of change from baseline to the next quarter across 4 groups of baseline serum ALP concentrations (reference: baseline serum ALP 80– <120 U/l and unchanged from Q1 to Q2).

In fully adjusted models, patients with a baseline ALP ≥ 80 U/l and who had an increase in ALP in the subsequent quarter had a significantly higher risk of mortality compared to the reference group. In addition, a decrease in ALP was associated with a higher risk of mortality in patients with a baseline ALP ≥ 120 U/l. In contrast, lower baseline ALP concentrations showed a trend toward lower mortality risk irrespective of the direction of change in ALP level in the subsequent quarter (fig. 5). In sensitivity analysis, an increase in ALP was associated with higher mortality risk compared to no change across all baseline ALP strata (online suppl. fig. 4).

Fig. 5. Association of change in serum ALP and all-cause mortality across strata of baseline concentration (case-mix and MICS-adjusted).

Table 5. All-cause mortality HRs in baseline serum ALP groups and their changes in 102,754 incident HD patients

Baseline ALP group, U/l	ALP change, U/l	n	Event rate*	Unadjusted		Case-mix adjusted		Case-mix and MICS-adjusted	
				HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<80	Decreased (<-10)	4,987	112	0.71 (0.66–0.77)	<0.0001	0.77 (0.72–0.83)	<0.0001	0.93 (0.87–1.00)	0.0598
	Unchanged (±10)	24,590	130	0.83 (0.80–0.87)	<0.0001	0.80 (0.77–0.84)	<0.0001	0.90 (0.87–0.94)	<0.0001
	Increased (>10)	12,448	168	1.08 (1.03–1.13)	0.0027	1.01 (0.96–1.06)	0.778	0.95 (0.91–1.00)	0.0631
80–<120	Decreased (<-10)	12,308	134	0.86 (0.82–0.90)	<0.0001	0.93 (0.88–0.97)	0.0021	1.00 (0.95–1.05)	0.9847
	Unchanged (±10)	14,990	156	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Increased (>10)	11,194	195	1.26 (1.20–1.32)	<0.0001	1.24 (1.18–1.30)	<0.0001	1.07 (1.03–1.13)	0.003
120–<160	Decreased (<-10)	6,297	158	1.02 (0.96–1.08)	0.5589	1.12 (1.06–1.19)	<0.0001	1.08 (1.02–1.14)	0.0131
	Unchanged (±10)	2,706	178	1.15 (1.07–1.24)	0.0003	1.21 (1.12–1.31)	<0.0001	1.04 (0.96–1.12)	0.3236
	Increased (>10)	3,481	246	1.58 (1.49–1.69)	<0.0001	1.66 (1.56–1.77)	<0.0001	1.24 (1.16–1.32)	<0.0001
≥160	Decreased (<-10)	6,009	209	1.34 (1.27–1.42)	<0.0001	1.54 (1.46–1.62)	<0.0001	1.15 (1.08–1.23)	<0.0001
	Unchanged (±10)	1,034	234	1.51 (1.35–1.68)	<0.0001	1.64 (1.47–1.83)	<0.0001	1.17 (1.04–1.30)	0.007
	Increased (>10)	2,710	317	2.04 (1.91–2.18)	<0.0001	2.21 (2.07–2.36)	<0.0001	1.19 (1.10–1.29)	<0.0001

* Per 1,000 patient-years.

Discussion

We evaluated the association of the change in concentration of 4 MBD markers, Phos, Ca_{Alb} , iPTH and ALP, during the first 6 months of maintenance HD with all-cause mortality in a cohort of 102,754 incident HD patients across strata of baseline MBD markers.

Changes deviating from KDOQI-recommended concentrations (Phos 3.5–<5.5 mg/dl, Ca_{Alb} 8.4–<9.5 mg/dl and iPTH 150–<300 pg/ml) were generally associated with higher mortality after adjustment for case-mix and MICS covariates [19]. In addition, both higher baseline and increased ALP ≥ 80 U/l concentrations showed a trend towards higher risk of mortality. These findings provide additional evidence for more precise management of CKD-MBD markers during the first 6 months of treatment.

Previous observational studies have highlighted the importance of adherence to the KDOQI-recommended levels of serum Phos, calcium and iPTH from the beginning of HD treatment, demonstrating additive effects gained by the achievement of the recommended target levels on patient survival [20, 21]. In addition, one study found that patients who achieved recommended ranges for a shorter duration of time had a higher risk of death [20]. Our results were conceptually in line with these studies. Moreover, this study provided further insight about mortality risk related to changes in serum CKD-MBD markers when stratified by their baseline levels.

An increased risk in mortality in the fully adjusted model was found in patients who deviated from baseline Ca_{Alb} 8.4–<9.5 mg/dl, as well as among patients who maintained a stable concentration of baseline Ca_{Alb} 9.5–<10.2 mg/dl. While these results provide support for the KDOQI guideline to maintain a lower normal range of Ca_{Alb} 8.4–<9.5 mg/dl, this opposes the KDIGO guidelines with its recommendations of normal Ca_{Alb} range as 8.6–10.2 mg/dl. It should be noted that this study population was composed of incident HD patients, and thus the optimal range may differ from maintenance HD [4, 11]. This is also the case for iPTH where the recommended normal range is 160–720 pg/ml. Among patients who experienced an increase in iPTH, baseline iPTH levels ≥ 150 pg/ml were incrementally associated with higher mortality. In addition, patients with lower iPTH concentrations at baseline and who experienced a further decrease in the subsequent quarter also exhibited a higher risk of mortality, which is consistent with previous reports and the KDOQI guidelines [4–9, 11, 12, 19].

Among the CKD-MBD parameters examined in this study, deviations in serum Phos concentrations at both extremes were associated with higher all-cause mortality. Higher concentrations as well as excessive changes from the recommended range (3.5–<5.5 mg/dl) were associated with higher mortality, and the risk was dependent on the differences in concentration from that range. Meanwhile, an increase in serum ALP concentration was associated with higher mortality risk across baseline strata of ALP ≥ 80 U/l. These results support the importance and robustness of serum ALP concentration as an MBD biomarker that predicts mortality [4–9, 11, 12, 19, 22]. Although associations between low ALP and mortality were not significant in our analyses, a previous study investigating the effect of change in ALP on mortality showed similar results. These findings suggest that the relationship of decreased ALP and mortality may be impacted by baseline ALP concentrations [6].

Several factors might have contributed to these findings and there are a number of limitations to this study. First, pre-dialysis care and patient condition may affect survival more potently than treatments administered after dialysis initiation in incident HD patients who bear the highest mortality risk [4, 6, 23]. Although we did adjust for the use of intravenously delivered vitamin D medications, data on other prescription, behavior and dietary interventions were not available in this study. We cannot analyze the impact of interventions such as phosphate binders, oral active or nutritional vitamin D dose, or surgical interventions such as parathyroidectomy on the associations between CKD-MBD markers and mortality. We also acknowledge that another limitation in this study is the inability to address other CKD-MBD-related factors in the blood such as fibroblast growth factor-23 or vitamin D metabolites. Despite rigorously adjusting for markers of malnutrition and inflammation, other variables namely C-reactive protein and dialysate calcium were unavailable in this cohort, and we cannot exclude residual confounding given the observational study design. Furthermore, we only evaluated changes during the first 6 months of dialysis treatment but not in the subsequent periods to focus on the immediate changes after dialysis initiation in CKD-MBD markers. Future studies are needed to investigate whether these associations differ according to dialysis vintage. Finally, cause of death was unavailable in our cohort.

Strengths of our study include a large nationally representative incident HD population with detailed patient level data, which allowed us to rigorously account

for a range of clinically relevant factors. Essentially all incident HD patients in the original cohort were included in our analyses, and thus the likelihood of selection bias is minimized. Additionally, all dialysis facilities were under uniform administrative care, and all laboratory tests were performed in one single laboratory with optimal quality assurance monitoring. We used quarterly averaged measurements rather than one single baseline measurement at to minimize effects of short-term variations. Furthermore, the relationship of CKD-MBD and mortality is multi-faceted and involves multiple MBD markers. In our fully adjusted models, we adjusted for the other MBD markers and their change aside from the exposure of interest, suggesting that our findings are independent of other MBD markers change and baseline measurements.

Conclusion

In conclusion, we demonstrated that baseline levels and changes in serum concentrations of CKD-MBD-related parameters in the first 6 months after initiation of HD treatment were differentially associated with all-cause mortality in patients with ESRD. Further studies are needed to evaluate whether stricter interventions to correct these abnormalities in the early period after HD initiation can improve patient survival.

Author Contributions

Study design: M.S., M.F., Y.O., E.S., C.M.R., C.P.K. and K.K.-Z. Study conduct: M.S., M.F., Y.O., E.S. and K.K.-Z. Data analysis: M.S., M.F. and E.S. Data interpretation: M.S., M.F., Y.O., E.S.,

C.M.R., W.L.L., J.W., V.A.R., S.B., C.P.K. and K.K.-Z. Drafting of the manuscript: M.S., M.F., Y.O., E.S., C.M.R., W.L.L., J.W., V.A.R., S.B., C.P.K. and K.K.-Z. Revising manuscript content: M.S., Y.O., E.S. and K.K.-Z. Approving final version of manuscript: M.S., M.F., Y.O., E.S., C.M.R., W.L.L., J.W., V.A.R., S.B., C.P.K. and K.K.-Z. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. K.K.-Z. takes responsibility for the integrity of the data analysis.

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References

- 1 Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A: 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. *J Am Soc Nephrol* 2004;15:770–779.
- 2 Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004;15:2208–2218.
- 3 Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, Akizawa T, Kurokawa K, Bommer J, Piera L, Port FK: Predictors and consequences of altered mineral metabolism: the dialysis outcomes and practice patterns study. *Kidney Int* 2005;67:1179–1187.
- 4 Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD: Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006;70:771–780.
- 5 Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, Young EW, Akizawa T, Akiba T, Pisoni RL, Robinson BM, Port FK: Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis* 2008;52:519–530.
- 6 Regidor DL, Kovesdy CP, Mehrotra R, Rambod M, Jing J, McAllister CJ, Van Wyck D, Kopple JD, Kalantar-Zadeh K: Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. *J Am Soc Nephrol* 2008;19:2193–2203.
- 7 Kalantar-Zadeh K, Miller JE, Kovesdy CP, Mehrotra R, Lukowsky LR, Streja E, Ricks J, Jing J, Nissenson AR, Greenland S, Norris KC: Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *J Bone Miner Res* 2010;25:2724–2734.

- 8 Rivara MB, Ravel V, Kalantar-Zadeh K, Streja E, Lau WL, Nissenson AR, Kestenbaum B, de Boer IH, Himmelfarb J, Mehrotra R: Uncorrected and albumin-corrected calcium, phosphorus, and mortality in patients undergoing maintenance dialysis. *J Am Soc Nephrol* 2015; 26:1671–1681.
- 9 Streja E, Wang HY, Lau WL, Molnar MZ, Kovesdy CP, Kalantar-Zadeh K, Park J: Mortality of combined serum phosphorus and parathyroid hormone concentrations and their changes over time in hemodialysis patients. *Bone* 2014;61:201–207.
- 10 Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, Appleby D, Nessel L, Belovich K, Chen J, Hamm L, Gadegbeku C, Horwitz E, Townsend RR, Anderson CA, Lash JP, Hsu CY, Leonard MB, Wolf M: Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011;79:1370–1378.
- 11 KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2009;113:S1–S130.
- 12 Steadon S, Sharples E: Renal association clinical practice guideline in mineral and bone disorders in CKD. *Nephron Clin Pract* 2011; 118(suppl 1):c145–c152.
- 13 Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, Komaba H, Ando R, Kakuta T, Fujii H, Nakayama M, Shibagaki Y, Fukumoto S, Fujii N, Hattori M, Ashida A, Iseki K, Shigematsu T, Tsukamoto Y, Tsubakihara Y, Tomo T, Hirakata H, Akizawa T: Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial* 2013;17:247–288.
- 14 Robinson BM, Zhang J, Morgenstern H, Bradbury BD, Ng LJ, McCullough KP, Gillespie BW, Hakim R, Rayner H, Fort J, Akizawa T, Tentori F, Pisoni RL: Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int* 2014;85:158–165.
- 15 Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K: Patterns and predictors of early mortality in incident hemodialysis patients: new insights. *Am J Nephrol* 2012;35:548–558.
- 16 Kuttykrishnan S, Kalantar-Zadeh K, Arah OA, Cheung AK, Brunelli S, Heagerty PJ, Katz R, Molnar MZ, Nissenson A, Ravel V, Streja E, Himmelfarb J, Mehrotra R: Predictors of treatment with dialysis modalities in observational studies for comparative effectiveness research. *Nephrol Dial Transplant* 2015;30: 1208–1217.
- 17 K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42:S1–S201.
- 18 Lukowsky LR, Molnar MZ, Zaritsky JJ, Sim JJ, Mucsi I, Kovesdy CP, Kalantar-Zadeh K: Mineral and bone disorders and survival in hemodialysis patients with and without polycystic kidney disease. *Nephrol Dial Transplant* 2012;27:2899–2907.
- 19 Belzeroff V, Goodman WG, Ren L, Kalantar-Zadeh K: Cinacalcet lowers serum alkaline phosphatase in maintenance hemodialysis patients. *Clin J Am Soc Nephrol* 2009;4: 673–679.
- 20 Danese MD, Belzeroff V, Smirnakis K, Rothman KJ: Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin J Am Soc Nephrol* 2008;3:1423–1429.
- 21 Cozzolino M, Messa P, Brancaccio D, Cannella G, Bolasco P, Di Luca M, Costanzo AM, Paparatti Ud, Festa V, Gualberti G, Mazzaferrero S: Achievement of NKF/K-DOQI recommended target values for bone and mineral metabolism in incident hemodialysis patients: results of the FARO-2 cohort. *Blood Purif* 2014;38:37–45.
- 22 Lau WL, Kalantar-Zadeh K, Kovesdy CP, Mehrotra R: Alkaline phosphatase: better than PTH as a marker of cardiovascular and bone disease? *Hemodial Int* 2014;18:720–724.
- 23 Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR: Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int* 2006;70:351–357.