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COMPARATIVE MORTALITY–PREDICTABILITY USING ALKALINE PHOSPHATASE AND PARATHYROID HORMONE IN PATIENTS ON PERITONEAL DIALYSIS AND HEMODIALYSIS

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♦ ***Background:*** **In hemodialysis (HD) patients, serum alkaline phosphatase (ALP) and parathyroid hormone (PTH) derangements are associated with mortality, but outcome-predictability using ALP and PTH in peritoneal dialysis (PD) patients remains uncertain.**

♦ ***Methods:*** **In a cohort of 9244 adult PD patients from a large national dialysis organization (entry period 2001 – 2006, with follow-up through 2009), we used multivariable Cox models adjusted for case-mix and laboratory covariates to examine the associations of time-averaged ALP and PTH with all-cause mortality. We then compared mortality-predictability using ALP and PTH in 9244 PD and 99 323 HD patients.**

♦ ***Results:*** **In PD patients, ALP concentrations exceeding 150 U/L were associated with increased mortality (reference ALP: 70 to <90 U/L). Hazard ratios (HRs) and 95% confidence intervals (CIs) were 1.18 (1.03 to 1.36), 1.27 (1.08 to 1.50), 1.49 (1.23 to 1.79), and 1.35 (1.19 to 1.53) for ALP concentrations of 150 to <170 U/L, 170 to <190 U/L, 190 to <210 U/L, and ≥210 U/L respectively. In contrast, we observed a U-shaped association between PTH concentration and death risk in PD patients, with PTH concentrations of less than 200 pg/mL and 700 pg/mL or more associated with increased mortality (reference PTH: 200 to <300 pg/mL). Hazard ratios and 95% CIs were 1.25 (1.12 to 1.41), 1.12 (1.02 to 1.23), 1.06 (0.96 to 1.18), 1.09 (0.97 to 1.24), 1.12 (0.97 to 1.29), 1.18 (0.99 to 1.40), and 1.23 (1.09 to 1.38) for PTH concentrations of <100 pg/mL, 100 to <200 pg/mL, 300 to <400 pg/mL, 400 to <500 pg/mL, 500 to <600 pg/mL, 600 to <700 pg/mL, and ≥700 pg/mL respectively. Compared with PD patients having serum concentrations of ALP and PTH within reference ranges, patients on HD experienced increased mortality across all ALP and PTH concentrations, particularly those in the lowest and highest categories.**

♦ ***Conclusions:*** **In summary, higher ALP concentrations are associated with increased mortality, and lower and higher PTH concentrations are both associated with death risk in PD patients. The utility of ALP in the management of chronic kidney disease mineral bone disorders in PD patients warrants further study.**

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End-stage renal disease patients, including those treated with peritoneal dialysis (PD), have an exceptionally high cardiovascular risk that is not wholly explained by

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traditional risk factors (1). In dialysis patients, chronic kidney disease mineral bone disorders (CKD-MBD) are exceedingly common and have been implicated as nontraditional risk factors for cardiovascular morbidity and mortality (2). Guidelines from Kidney Disease Improving Global Outcomes recommend serum alkaline phosphatase (ALP) and parathyroid hormone (PTH) as adjunctive tests in the assessment of bone turnover, and mounting evidence suggests that derangements in these biomarkers are associated with coronary artery calcification, cardiovascular events, sudden cardiac death, and increased mortality in non-dialysis-dependent CKD and hemodialysis (HD) patients (3–14). However, controversy remains about whether there is additive value for ALP in addition to PTH in CKD-MBD management (15–17).

Serum ALP is a metalloenzyme with wide tissue distribution, but with particularly high concentrations in bone, liver, intestine, and placenta (18). The bone isoform of ALP is produced by osteoblasts and may be a more specific indicator of bone turnover than is PTH, which originates from the parathyroid glands and is influenced by age, race, suboptimal assays, inflammation, and nutrition and anthropometric status (19–23). Experimental data suggest that ALP may be causally associated with vascular calcification via hydrolysis of pyrophosphate, a potent calcification inhibitor (18,24,25). Vascular calcification is a measure of atherosclerotic burden and—through effects on arterial compliance, pulse pressure, and afterload—might also contribute to ventricular hypertrophy and impaired coronary perfusion (26). Moreover, it is highly correlated with cardiovascular morbidity and mortality in dialysis patients (27). Based on those data, ALP derangements might be inferred to be an important risk factor for mortality in dialysis patients.

Data from the US Renal Data System show that the incident PD population is rapidly growing and now accounts for 7% of dialysis patients (28). It is plausible that bone metabolism and morphology may be inherently different in PD and HD patients because of the heightened risk of vitamin D deficiency associated with peritoneal effluent losses and because of differences in CKD-MBD management in PD—specifically, greater use of oral vitamin D in lieu of intravenous forms (29). To date, few studies have examined the associations of ALP and PTH with mortality in PD patients.

We hypothesized that ALP and PTH derangements are associated with mortality in both PD and HD patients. We conducted the present study to examine the associations of serum ALP and PTH concentrations with mortality in PD patients, and to compare mortality-predictability using those markers in HD and PD patients in a large contemporary cohort of dialysis patients having detailed laboratory data and extended follow-up over which to observe outcomes.

METHODS

STUDY POPULATION

We examined data for all end-stage renal disease patients undergoing HD or PD in one of the DaVita outpatient dialysis facilities from 1 July 2001 to 30 June 2006. Patients were followed for outcomes through 30 June 2009. Each patient's baseline quarter was the calendar quarter of entry into the cohort, and the ascribed dialysis modality was the modality in use in the baseline quarter. Patients were included provided that they were 18 years of age or older, had 1 or more ALP and PTH measurements in the baseline quarter, and had no missing data for key covariates or for follow-up time.

The study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and DaVita Clinical Research. Given the large sample size, the anonymity of the study patients, and the nonintrusive nature of the research, requirement for consent was exempted.

SOCIODEMOGRAPHIC, COMORBIDITY, AND LABORATORY MEASUREMENTS

The creation of the cohort has previously been described (30). To minimize measurement variability, all repeated clinical and laboratory measurements for each patient during any 13-week calendar quarter were averaged for up to 20 entry calendar quarters (1 July 2001 through 30 June 2006), and summary estimates were used in all models. Sociodemographic information and presence of diabetes were obtained from the DaVita database.

Data on baseline comorbidities were obtained by linking the DaVita database to US Renal Data System Medical Evidence Form 2728 data, and the results were categorized into these cardiovascular comorbidities: congestive heart failure, peripheral vascular disease, atherosclerotic heart disease, and other cardiovascular diseases.

In all DaVita dialysis clinics, blood samples were drawn using standardized techniques and were transported to the DaVita laboratory in Deland, Florida, typically within 24 hours, where they were measured using automated and standardized methods. Most laboratory parameters, including serum ALP, were measured monthly, and serum intact PTH was measured at least quarterly using a first-generation immunoradiometric PTH assay (Nichols, San Juan Capistrano, CA, USA) (31).

EXPOSURE ASCERTAINMENT

In co-primary analyses, we examined how ALP and PTH concentrations, separately, were associated with all-cause mortality. Serum ALP was divided into 10 *a priori* categories: <50 U/L, 50 to <70 U/L, 70 to <90 U/L, 90 to <110 U/L, 110 to <130 U/L, 130 to <150 U/L, 150 to <170 U/L, 170 to <190 U/L, 190 to <210 U/L, and ≥210 U/L. Serum PTH was divided into 8 *a priori* categories: <100 pg/mL, 100 to <200 pg/mL, 200 to <300 pg/mL, 300 to <400 pg/mL, 400 to <500 pg/mL, 500 to <600 pg/mL, 600 to <700 pg/mL, and ≥700 pg/mL. In secondary analyses, we examined mortality-predictability using low ALP (<120 U/L) compared with high ALP (≥120 U/L) within strata of low PTH (<300 pg/mL) and high PTH (≥300 pg/mL). The ALP cut-off was selected based on the threshold above which increased morbidity and mortality have been observed in earlier studies (11,12,32), and the PTH cut-off was selected based on the threshold above which treatment of secondary hyperparathyroidism is recommended in the Kidney Disease Outcomes Quality Initiative guidelines (33).

OUTCOME ASCERTAINMENT

The outcome of interest was all-cause death ascertained from the DaVita database and the US Renal Data System database linkage. Patients were followed for the outcome of interest until death or censoring for transplantation, transfer to a non-DaVita dialysis clinic, or end of the study (30 June 2007).

STATISTICAL ANALYSES

Baseline characteristics of the patients with high and low ALP within the strata of high and low PTH were compared using analysis of variance, Kruskal–Wallis, and chi-square tests as dictated by data type. The associations of baseline and time-averaged ALP with mortality in PD patients were examined using Cox proportional hazards regression. Pooled analyses were used to evaluate the mortality-predictability for baseline and time-averaged ALP in HD and PD patients. Analogous analyses were used to examine the associations of baseline and time-averaged serum PTH with mortality in PD patients, and to compare mortality-predictability using baseline and time-averaged PTH in HD and PD patients.

For each analysis, three sequential models, with incremental multivariable adjustment for baseline covariates, were examined:

- Unadjusted models included the exposure of interest and the entry calendar quarter (to account for ALP and PTH assay drift)
- Case-mix adjusted models included all covariates in the unadjusted models, plus age, sex, race or ethnicity (non-Hispanic African American, non-Hispanic white, Hispanic, and Asian, with the first two groups hereafter referred to as "black" and "white" respectively), diabetes, baseline cardiovascular comorbidities, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin
- Case-mix plus laboratory-adjusted models ("fully-adjusted") included all covariates in the case-mix adjusted models, plus laboratory surrogates of nutrition and inflammation (serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate), calcium, phosphorus, hemoglobin, and weekly dose of an erythropoiesis-stimulating agent

Given that elevated ALP concentrations can also be observed with liver disease, the fully-adjusted analyses of ALP and mortality were repeated with additional adjustment for serum aspartate aminotransferase (AST) as sensitivity analyses. Missing covariate data were imputed as appropriate. Plots of log[–log(survival rate)] against log(survival time) were used to check the proportionality assumption. All calculations were conducted using the SAS software application (version 9.1: SAS Institute, Cary, NC, USA) and Stata MP (version 10.1: StataCorp LP, College Station, TX, USA).

RESULTS

COHORT DESCRIPTION

After excluding patients not on PD or HD during the baseline quarter, less than 18 years of age, or with missing data for ALP, PTH, key covariates, or follow-up time, the final study cohort consisted of 108 567 patients among whom 9244 were on PD and 99 323 were on HD (Figure 1). Examination of meaningful differences in baseline characteristics for the included and excluded patients receiving dialysis during the baseline quarter demonstrated that those who were excluded were less likely to be black or Hispanic or to receive Medicare or Medicaid; likely to be white and to have a shorter dialysis vintage and atherosclerotic heart disease; and likely to have lower mean creatinine and ferritin concentrations (Table 1).

Concentrations of ALP were similar in PD and HD patients, and more than 60% of the patients using either treatment modality had an ALP concentration less than 110 U/L [typical reference range: 25 – 100 U/L (34);

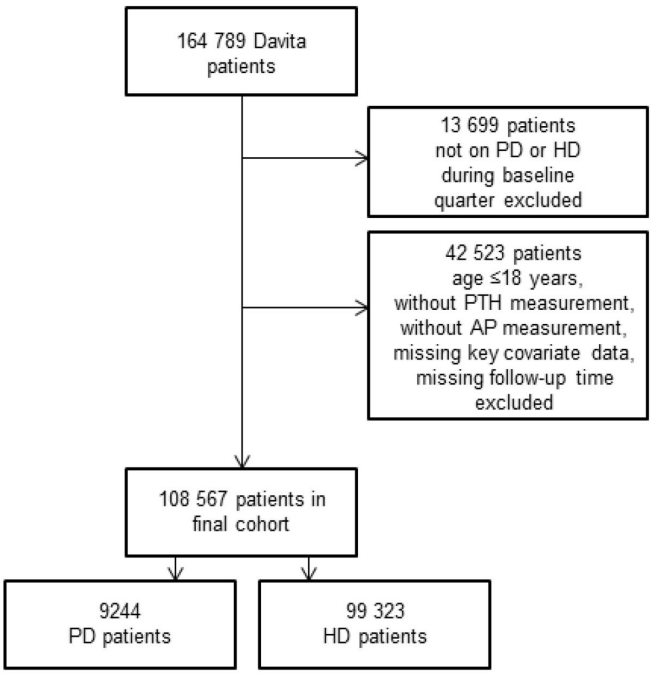

Figure 1 — Study cohort creation. PD = peritoneal dialysis; HD = hemodialysis; PTH = parathyroid hormone; AP = alkaline phosphatase.

Figure 2]. However, PD patients manifested a higher prevalence of PTH exceeding 300 pg/dL (48.1% vs 39.4% of HD patients) and PTH exceeding 600 pg/dL (20.1% vs 13.8% of HD patients). Compared with HD treatment, PD treatment was associated with a higher risk of having a PTH concentration exceeding 300 pg/dL or exceeding 600 pg/dL after adjustment for case-mix and laboratory covariates [odd ratios (95% confidence intervals): 1.68 (1.60 to 1.76) and 1.73 (1.62 – 1.84) respectively; Table 2].

In terms of baseline characteristics, patients with high turnover markers (concordantly high ALP and PTH) were more likely to be younger, female, black, and of longer dialysis vintage. They were less likely to be white or diabetic, or to have atherosclerotic heart disease, and they had higher mean creatinine and ferritin concentrations than did patients with low turnover markers (concordantly low ALP and PTH, Table 3).

ALP AND MORTALITY IN PD PATIENTS

The median follow-up time for the cohort was 2.7 years (interquartile range: 1.3 – 4.3 years), during which time

TABLE 1
Baseline Characteristics for the Included and Excluded Patients[a] Receiving Dialysis in the Baseline Quarter

Variable	Overall cohort			Peritoneal dialysis			Hemodialysis		
	Included	Excluded	*p* Value	Included	Excluded	*p* Value	Included	Excluded	*p* Value
Patients (*n*)	108 567	42 523		9 244	3 490		99 323	39 033	
Mean age (years)	60±16	59±17	<0.001	54±15	49±20	<0.001	60±16	60±17	0.8
Sex (% female)	46	44	<0.001	48	46	0.2	45	44	<0.001
Race or ethnicity (%)									
White	41	50	<0.001	51	55	<0.001	41	49	<0.001
Black	32	29	<0.001	24	25	<0.001	33	29	<0.001
Hispanic	15	10	<0.001	13	10	<0.001	16	10	<0.001
Asian	3	3	<0.001	4	3	<0.001	3	3	<0.001
Other	7	6	<0.001	6	5	<0.001	7	6	<0.001
Mean body mass index	26.9±6.9	26.9±7.3	0.004	26.4±6.0	25.8±7.1	0.003	26.9±7.0	27.0±7.3	0.05
Active tobacco use (%)	5	5	<0.001	6	4	<0.001	5	5	0.008
Comorbidities (%)									
Diabetes	57	55	<0.001	49	43	<0.001	58	56	<0.001
CHF	27	28	<0.001	16	16	<0.001	28	29	<0.001
AHD	20	23	<0.001	15	15	<0.001	21	23	<0.001
PVD	11	12	<0.001	8	8	<0.001	11	12	0.02
Other cardiac disease	5	7	<0.001	4	4	<0.001	6	7	<0.001

TABLE 1 (cont'd)

Variable	Overall cohort Included	Overall cohort Excluded	*p* Value	Peritoneal dialysis Included	Peritoneal dialysis Excluded	*p* Value	Hemodialysis Included	Hemodialysis Excluded	*p* Value
Dialysis vintage (%)									
3 to <6 Months	57	47	<0.001	49	31	<0.001	57	43	<0.001
6 Months to <2 years	17	22	<0.001	17	19	0.09	17	25	<0.001
2 to <5 Years	17	19	<0.001	18	25	<0.001	16	21	<0.001
≥5 Years	10	12	<0.001	15	25	<0.001	9	12	<0.001
Primary insurance (%)									
Medicare	68	67	<0.001	68	69	0.1	68	69	0.003
Medicaid	8	4	<0.001	3	4	0.01	6	4	<0.001
Other	26	29	<0.001	29	27	0.03	26	27	<0.001
Marital status (%)									
Married	49	51	<0.001	60	51	<0.001	48	51	<0.001
Single	8	7	>0.9	9	7	<0.001	8	7	<0.001
Divorced	28	28	<0.001	23	35	0.002	28	27	<0.001
Widowed	15	14	<0.001	8	8	0.05	16	15	<0.001
Laboratory variables									
Ferritin (ng/mL)									
Median	379	343	<0.001	275	295	<0.001	389	354	<0.001
IQR	177–712	166–649		122–586	131–582		183–723	174–652	
Hemoglobin (g/dL)	12.1±1.4	11.9±1.5	<0.001	12.0±1.5	11.9±1.6	<0.001	12.1±1.4	11.9±1.5	<0.001
Serum albumin (g/dL)	3.7±0.5	3.5±0.6	<0.001	3.6±0.5	3.6±0.6	0.02	3.7±0.5	3.5±0.6	<0.001
TIBC (µg/dL)	211.0±46.5	207.0±51.9	<0.001	230.0±53.6	225.0±55.4	0.004	210.0±45.5	205.0±51.1	<0.001
Bicarbonate (mmol/L)	22.5±3.1	22.8±3.4	<0.001	24.3±3.4	24.1±3.5	0.01	22.3±3.0	22.7±3.4	<0.001
Serum creatinine (mg/dL)	8.2±3.4	7.2±3.4	<0.001	8.6±3.7	8.3±3.7	<0.001	8.2±3.3	7.0±3.3	<0.001
WBC count ($\times 10^9$/L)	7.4±2.5	7.8±2.9	<0.001	7.5±2.6	7.6±2.7	0.3	7.4±2.4	7.8±3.0	<0.001
Lymphocytes (%)	20.6±7.8	19.6±8.5	<0.001	19.8±7.7	21.1±9.4	<0.001	20.7±7.8	19.5±8.4	<0.001
Calcium (mg/dL)	9.2±0.7	9.2±0.8	<0.001	9.2±0.8	9.2±0.9	0.1	9.2±0.7	9.2±0.8	<0.001
Phosphorus (mg/dL)	5.6±1.5	5.4±1.6	<0.001	5.4±1.5	5.5±1.7	<0.001	5.6±1.5	5.4±1.6	<0.001

CHF = congestive heart failure; AHD = atherosclerotic heart disease; PVD = peripheral vascular disease; IQR = interquartile range; TIBC = total iron binding capacity; WBC = white blood cell.

[a] Does not consider patients with unknown modality, loss to follow-up, renal recovery, death, or transplantation during the baseline quarter.

[b] Data are presented as means ± standard deviation or proportions, unless otherwise indicated. Significance testing performed by 2-sample t-tests, Wilcoxon rank-sum tests, or chi-square tests.

56 005 all-cause deaths occurred. In analyses considering baseline measurements, higher ALP concentrations were associated with increased mortality among PD patients in the unadjusted, case-mix, and fully-adjusted analyses [Figure 3(A), Table 4]. In the fully-adjusted analyses, ALP concentrations less than 50 U/L were associated with lower mortality, and ALP concentrations exceeding 90 U/L were associated with higher mortality (reference ALP: 70 to <90 U/L). Sensitivity analyses adjusted for AST were qualitatively similar (Table 5). When the data were examined in quintiles, a graded association between higher ALP quintile and mortality was evident (Figure 4).

In fully-adjusted analyses considering time-averaged measurements, we observed a J-shaped association between ALP concentration and mortality in PD patients [Figure 3(B), Table 4]. Concentrations of ALP less than

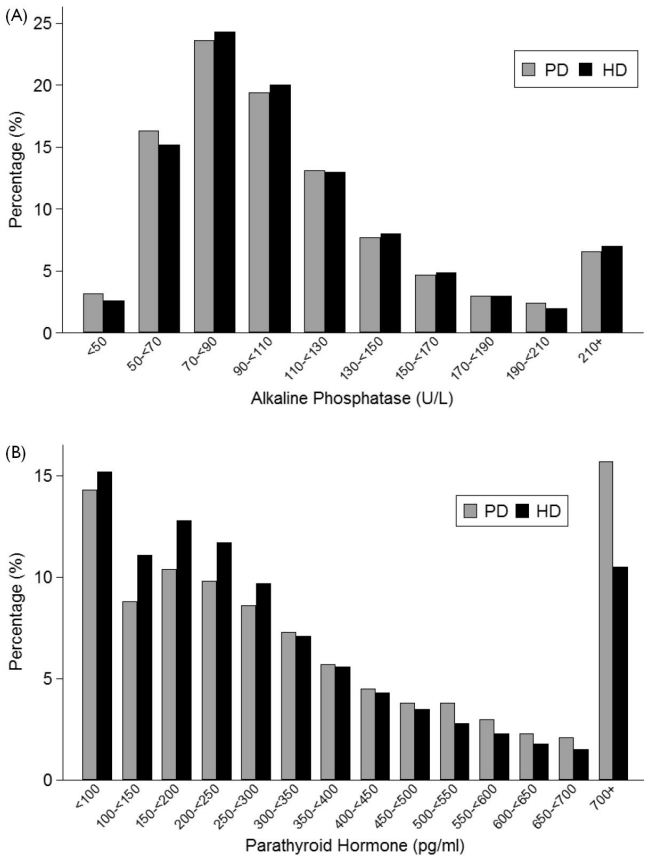

Figure 2 — Distribution of (A) baseline serum alkaline phosphatase and (B) parathyroid hormone concentrations in the peritoneal dialysis (PD) and hemodialysis (HD) patients.

TABLE 2
Odds Ratio of a Baseline Serum Parathyroid Hormone (PTH) Concentration Exceeding the Clinically Relevant Threshold in Peritoneal Dialysis Patients (*n*=9 422) Compared with Hemodialysis Patients (*n*=99 323).

Baseline PTH	Odds ratio (95% confidence interval) Unadjusted[a]	Multivariable adjusted[b]
>300 pg/dL	1.43 (1.37 to 1.49)	1.68 (1.60 to 1.76)
>600 pg/dL	1.55 (1.47 to 1.64)	1.73 (1.62 to 1.84)

[a] Included dialysis modality and entry calendar quarter.
[b] Included case-mix model covariates, plus body mass index, ferritin, serum albumin, total iron binding capacity, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, hemoglobin, calcium, phosphorus, and alkaline phosphatase.

70 U/L were not associated with lower mortality, but ALP concentrations exceeding 150 U/L were associated with higher mortality (reference ALP: 70 to <90 U/L). Sensitivity analyses adjusted for AST were qualitatively similar (Table 5).

When baseline ALP and PTH concentrations were jointly considered (with patients having concordantly low ALP and PTH as the reference), mortality was increased in patients with high ALP regardless of PTH stratum, but patients with low ALP and high PTH were not at increased risk (Table 6).

PTH AND MORTALITY IN PD PATIENTS

In analyses considering baseline measurements, the associations of PTH concentrations with all-cause mortality in PD patients varied in the unadjusted, case-mix, and fully-adjusted analyses [Figure 5(A), Table 4]. In fully-adjusted analyses, higher PTH and mortality were not significantly associated. However, when examined in quintiles, a J-shaped association between higher PTH quintile and mortality was observed (Figure 4).

In analyses considering time-averaged measurements, the associations of PTH concentrations with all-cause mortality in PD patients varied in the unadjusted, case-mix, and fully-adjusted analyses [Figure 5(B), Table 4]. In fully-adjusted analyses, we observed a U-shaped PTH–mortality association in which PTH concentrations less than 200 pg/mL and 600 pg/mL or greater were associated with increased mortality (reference PTH: 200 to <300 pg/mL).

MORTALITY-PREDICTABILITY USING ALP AND PTH IN HD AND PD PATIENTS

Among HD and PD patients, the mortality-predictability using ALP concentrations was compared in fully-adjusted analyses. In analyses of baseline ALP values (PD patients with ALP 70 to <90 U/L being the reference), incrementally higher ALP values showed a relatively linear association with mortality in HD and PD patients alike [Figure 6(A), Table 7]. In analyses of time-averaged ALP measurements, HD patients experienced increased mortality at all concentrations, with the greatest risk occurring in the highest and lowest ALP categories. In contrast, PD patients experienced increased mortality with ALP values exceeding 150 U/L [Figure 6(B), Table 7]. Sensitivity analyses adjusted for AST were qualitatively similar (Table 8).

In HD and PD patients, the mortality-predictability using PTH concentrations was compared in fully-adjusted analyses (PD patients having a PTH value of 200 to <300 pg/mL being the reference group). In analyses of baseline PTH values, we observed a relatively linear association between higher PTH and mortality in HD patients; in PD patients, the lowest PTH category was associated with a survival benefit [Figure 7(A), Table 7]. In analyses of time-averaged PTH measurements, HD

TABLE 3
Baseline Characteristics of 9244 Peritoneal Dialysis Patients by Baseline Serum Alkaline Phosphatase and Parathyroid Hormone

	Serum alkaline phosphatase			
	<120 U/L		≥120 U/L	
	Serum parathyroid hormone		Serum parathyroid hormone	
Variable	<300 pg/mL	≥300 pg/mL	<300 pg/mL	≥300 pg/mL
Patients (*n*)	3631	2792	1173	1648
Mean age (years)	57±15	52±16	56±15	49±15
Women (%)	45	45	53	56
Race or ethnicity (%)				
White	58	46	55	40
Black	18	30	17	34
Hispanic	13	12	16	15
Asian	5	5	3	4
Other	6	6	8	6
Mean BMI	26.4±5.8	26.7±6.0	25.6±5.7	26.3±6.4
Active tobacco use (%)	5	5	6	6
Comorbidities (%)				
Diabetes	51	41	67	48
CHF	16	12	21	16
AHD	17	11	18	14
PVD	9	5	11	7
Other cardiac disease	5	3	4	3
Vintage (%)				
3 to <6 Months	7	8	8	8
6 to <24 Months	30	27	30	21
2 to <5 Years	38	36	34	33
≥5 Years	25	29	28	38
Primary insurance (%)				
Medicare	68	64	75	69
Medicaid	2	3	3	4
Other	30	33	22	26
Marital status (%)				
Married	64	60	59	50
Single	18	25	23	31
Divorced	8	8	9	11
Widowed	10	7	9	8
Laboratory variables				
Ferritin (ng/mL)				
Median	260	253	352	316
IQR	116,549	118,536	141,678	125,664
Hemoglobin (g/dL)	12.1±1.4	11.9±1.5	12.1±1.5	11.9±1.5
Serum albumin (g/dL)	3.6±0.4	3.7±0.5	3.4±0.5	3.6±0.5
TIBC (µg/dL)	235.0±53.1	232.0±51.5	219.0±58.1	223.0±53.9
Bicarbonate (mmol/L)	24.8±3.3	24.1±3.3	24.2±3.5	23.5±3.5
Serum creatinine (mg/dL)	8.2±3.5	9.6±3.8	7.2±3.0	9.0±3.6
WBC count ($\times 10^9$/L)	7.5±2.4	7.3±2.2	8.2±3.6	7.5±2.6
Lymphocytes (%)	19.3±7.4	20.0±8.0	18.4±7.5	20.1±8.0
Calcium (mg/dL)	9.3±0.7	9.2±0.8	9.1±0.8	9.2±0.9
Phosphorus (mg/dL)	5.1±1.4	5.8±1.6	5.0±1.4	5.7±1.6

BMI = body mass index; CHF = congestive heart failure; AHD = atherosclerotic heart disease; PVD = peripheral vascular disease; IQR = interquartile range; TIBC = total iron-binding capacity; WBC = white blood cell.

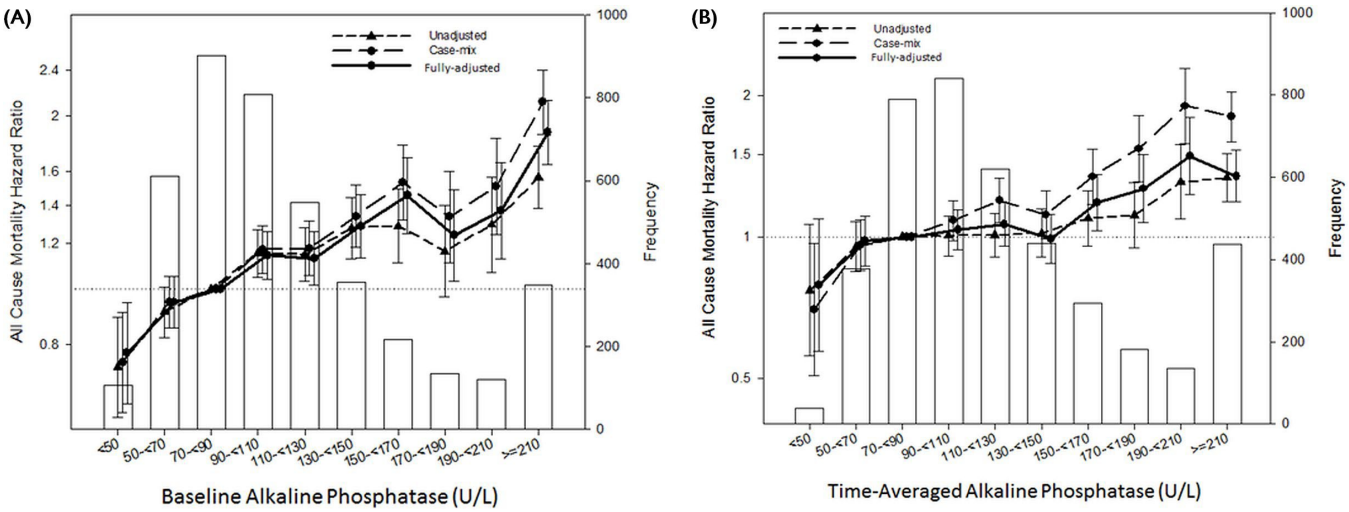

Figure 3 — All-cause mortality hazard ratios for (A) baseline and (B) time-averaged serum alkaline phosphatase in 9244 peritoneal dialysis patients. Unadjusted models included the exposure of interest and entry calendar quarter. Case-mix adjusted models included unadjusted model covariates, plus age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin. Fully-adjusted models included case-mix model covariates, plus serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agents.

TABLE 4
Hazard Ratios (HRs) for All-Cause Mortality by Baseline and Time-Averaged Serum Alkaline Phosphatase (ALP) and Parathyroid Hormone (PTH) Concentrations in 9244 Peritoneal Dialysis Patients

Serum concentration group	Baseline concentration						Time-averaged concentration					
	Unadjusted[a]		Case-mix adjusted[b]		Fully-adjusted[c]		Unadjusted[a]		Case-mix adjusted[b]		Fully-adjusted[c]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ALP (U/L)												
<50	0.73	0.60 to 0.90	0.75	0.61 to 0.91	0.77	0.63 to 0.95	0.77	0.56 to 1.06	0.70	0.51 to 0.97	0.79	0.57 to 1.09
50 to <70	0.91	0.82 to 1.01	0.95	0.86 to 1.05	0.95	0.86 to 1.05	0.95	0.84 to 1.08	0.96	0.85 to 1.09	0.98	0.87 to 1.11
70 to <90	Reference		Reference		Reference		Reference		Reference		Reference	
90 to <110	1.16	1.05 to 1.27	1.17	1.07 to 1.29	1.15	1.04 to 1.26	1.01	0.91 to 1.11	1.09	0.98 to 1.20	1.04	0.94 to 1.14
110 to <130	1.15	1.03 to 1.28	1.18	1.06 to 1.31	1.13	1.02 to 1.26	1.01	0.91 to 1.12	1.20	1.08 to 1.33	1.06	0.96 to 1.18
130 to <150	1.28	1.13 to 1.45	1.34	1.18 to 1.52	1.29	1.14 to 1.46	1.02	0.91 to 1.15	1.12	0.99 to 1.26	0.99	0.88 to 1.12
150 to <170	1.29	1.11 to 1.49	1.53	1.32 to 1.78	1.46	1.25 to 1.69	1.10	0.96 to 1.25	1.34	1.17 to 1.54	1.18	1.03 to 1.36
170 to <190	1.16	0.97 to 1.40	1.34	1.11 to 1.60	1.24	1.03 to 1.49	1.11	0.95 to 1.31	1.54	1.31 to 1.82	1.27	1.08 to 1.50

TABLE 4 (cont'd)

Serum concentration group	Baseline concentration						Time-averaged concentration					
	Unadjusted[a]		Case-mix adjusted[b]		Fully-adjusted[c]		Unadjusted[a]		Case-mix adjusted[b]		Fully-adjusted[c]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
190 to <210	1.29	1.07 to 1.57	1.51	1.24 to 1.83	1.37	1.13 to 1.66	1.31	1.09 to 1.57	1.90	1.58 to 2.29	1.49	1.23 to 1.79
≥210	1.57	1.38 to 1.77	2.12	1.86 to 2.40	1.87	1.65 to 2.13	1.34	1.19 to 1.50	1.80	1.59 to 2.04	1.35	1.19 to 1.53
PTH (pg/mL)												
<100	1.08	0.97 to 1.19	0.99	0.89 to 1.09	0.92	0.83 to 1.03	1.72	1.53 to 1.93	1.43	1.28 to 1.61	1.25	1.12 to 1.41
100 to <200	1.03	0.93 to 1.13	1.03	0.93 to 1.14	0.98	0.89 to 1.09	1.30	1.18 to 1.42	1.14	1.04 to 1.25	1.12	1.02 to 1.23
200 to <300	Reference		Reference		Reference		Reference		Reference		Reference	
300 to <400	0.88	0.79 to 0.98	0.99	0.89 to 1.11	0.96	0.85 to 1.07	0.92	0.82 to 1.02	1.09	0.98 to 1.21	1.06	0.96 to 1.18
400 to <500	0.85	0.74 to 0.97	1.08	0.94 to 1.23	1.08	0.94 to 1.23	0.87	0.77 to 0.98	1.13	1.00 to 1.28	1.09	0.97 to 1.24
500 to <600	0.87	0.76 to 1.00	1.11	0.97 to 1.28	1.05	0.91 to 1.21	0.88	0.77 to 1.02	1.22	1.06 to 1.40	1.12	0.97 to 1.29
600 to <700	0.74	0.63 to 0.88	1.05	0.88 to 1.24	0.96	0.81 to 1.14	0.80	0.68 to 0.95	1.26	1.06 to 1.50	1.18	0.99 to 1.40
≥700	0.73	0.65 to 0.82	1.15	1.02 to 1.28	1.03	0.92 to 1.16	0.82	0.74 to 0.92	1.43	1.28 to 1.60	1.23	1.09 to 1.38

CI = confidence interval.

[a] Included the exposure of interest and entry calendar quarter.

[b] Included unadjusted model covariates, plus age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin.

[c] Included case-mix model covariates, plus serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly erythropoietin-stimulating agent dose.

patients experienced increased mortality at all PTH concentrations, with the greatest risk occurring in the lowest and highest PTH categories. In contrast, PD patients experienced increased mortality in the lowest and highest PTH categories only [Figure 7(B), Table 7].

DISCUSSION

In this large, contemporary cohort of PD patients, we examined associations between biochemical markers of bone turnover and all-cause mortality. In analyses of baseline and time-averaged measurements, we found a significant association between higher serum ALP and mortality in PD patients that remained robust in multiple secondary and sensitivity analyses. We also observed a U-shaped association between time-averaged PTH and mortality in PD patients.

Elevated serum ALP might contribute to increased mortality by several mechanisms. Although found in a diverse set of tissues, ALP, when elevated, is commonly considered a marker of high bone turnover in dialysis patients (3,18). However, increasing evidence suggests

TABLE 5
Hazard Ratios (HRs) for All-Cause Mortality by Baseline and Time-Averaged Serum Alkaline Phosphatase (ALP) in 9244 Peritoneal Dialysis Patients with Additional Adjustment for Serum Aspartate Aminotransferase[a]

Serum ALP concentration group (U/L)	Baseline concentration		Time-averaged concentration	
	HR	95% CI	HR	95% CI
<50	0.77	0.63 to 0.95	0.79	0.57 to 1.10
50 to <70	0.95	0.86 to 1.05	0.98	0.87 to 1.11
70 to <90	Reference		Reference	
90 to <110	1.15	1.04 to 1.26	1.04	0.94 to 1.14
110 to <130	1.13	1.02 to 1.26	1.06	0.95 to 1.18
130 to <150	1.29	1.14 to 1.46	0.99	0.88 to 1.11
150 to <170	1.46	1.25 to 1.70	1.18	1.03 to 1.35
170 to <190	1.25	1.04 to 1.50	1.26	1.07 to 1.48
190 to <210	1.37	1.13 to 1.67	1.49	1.23 to 1.79
≥210	1.89	1.65 to 2.15	1.33	1.17 to 1.51

CI = confidence interval.

[a] Models included serum ALP concentration, entry calendar quarter, age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, serum albumin, ferritin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, weekly dose of erythropoiesis-stimulating agent, and serum aspartate aminotransferase.

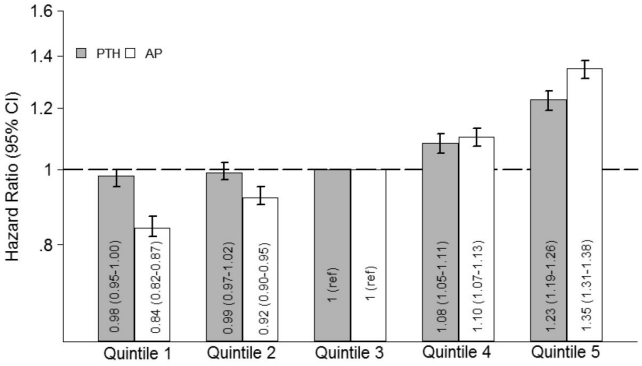

Figure 4 — All-cause mortality hazard ratios, with 95% confidence intervals (CIs), for baseline alkaline phosphatase (AP) and parathyroid hormone (PTH) quintiles in 9244 peritoneal dialysis patients. The Cox regression models included the exposure of interest, entry calendar quarter, age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, ferritin, serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agents.

that ALP is not simply a marker of poor bone health, but that it might also be a mediator of vascular calcification, which is a predictor of mortality in dialysis patients (18,24,25). In animal studies, nonspecific ALP has been shown to hydrolyze pyrophosphate, which is a potent inhibitor of vascular calcification that prevents incorporation of inorganic phosphate into hydroxyapatite crystals (24,25). Alkaline phosphatase has been shown to be upregulated in calcified diabetic arteries and in the blood vessels of kidney disease patients with calciphylaxis (35,36). In animal models, genetic ablation of tissue-nonspecific ALP has been shown to ameliorate vascular calcification (37). Additionally, levamisole, a nonspecific ALP inhibitor, has been shown to reduce the hydrolysis rate of pyrophosphate in uremic rat aortas (25). Emerging data demonstrating an association between ALP and coronary artery calcification, cardiovascular hospitalization, cardiovascular events, and sudden cardiac death in HD patients further corroborate a link between ALP and cardiovascular disease (6,12–14,25). Other potential mechanisms by which elevation of ALP might be associated with cardiovascular morbidity and mortality include 25-hydroxyvitamin D deficiency and inflammation (38,39).

To our knowledge, the present study is the first to show that ALP elevations are associated with increased mortality in PD patients. Many, but not all, studies (40,41) show that increased ALP is associated with greater mortality across heterogeneous groups including HD patients, kidney transplant recipients, non-dialysis-dependent CKD patients, and the general population (4–6,8,10,11,13,32,42–45). In contrast, Filipowicz *et al.* (40) and Yeoh and Sivaraman (41) recently demonstrated that skeletal ALP is not associated with increased serum C-reactive protein or death in CKD and non-CKD cohorts, suggesting that bone disease is unlikely to account for the observed associations of ALP with inflammation and mortality. However, the low representation of participants with advanced CKD in the aforementioned studies limits generalizability of the results to dialysis populations, and it is plausible that the associations between skeletal ALP and mortality may be different in PD patients than in individuals with lesser degrees of kidney dysfunction. In the only prior study to examine the ALP–mortality association in PD patients, baseline ALP greater than 130 U/L was not associated with 6-month mortality by logistic regression (41); however, interpretation of those data is limited by small sample size, short-term follow-up and inattention to finer gradations of ALP, and

TABLE 6
All-Cause Mortality by Baseline Serum Alkaline Phosphatase and Parathyroid Hormone in 9244 Peritoneal Dialysis Patients

Variable	Unadjusted[a] HR	Unadjusted[a] 95% CI	Case-mix adjusted[b] HR	Case-mix adjusted[b] 95% CI	Fully adjusted[c] HR	Fully adjusted[c] 95% CI
Alkaline phosphatase < 120 U/L						
Parathyroid hormone						
<300 pg/mL	Reference		Reference		Reference	
≥300 pg/mL	0.80	0.74 to 0.86	1.05	0.97 to 1.14	1.01	0.93 to 1.10
Alkaline phosphatase ≥ 120 U/L						
Parathyroid hormone						
<300 pg/mL	1.49	1.36 to 1.63	1.50	1.37 to 1.65	1.39	1.26 to 1.52
≥300 pg/mL	0.98	0.90 to 1.07	1.42	1.30 to 1.56	1.35	1.23 to 1.48

HR = hazard ratio; CI = confidence interval.

[a] Models included the exposure of interest and entry calendar quarter.

[b] Models included unadjusted model covariates, plus age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin.

[c] Models included case-mix model covariates, plus serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agents.

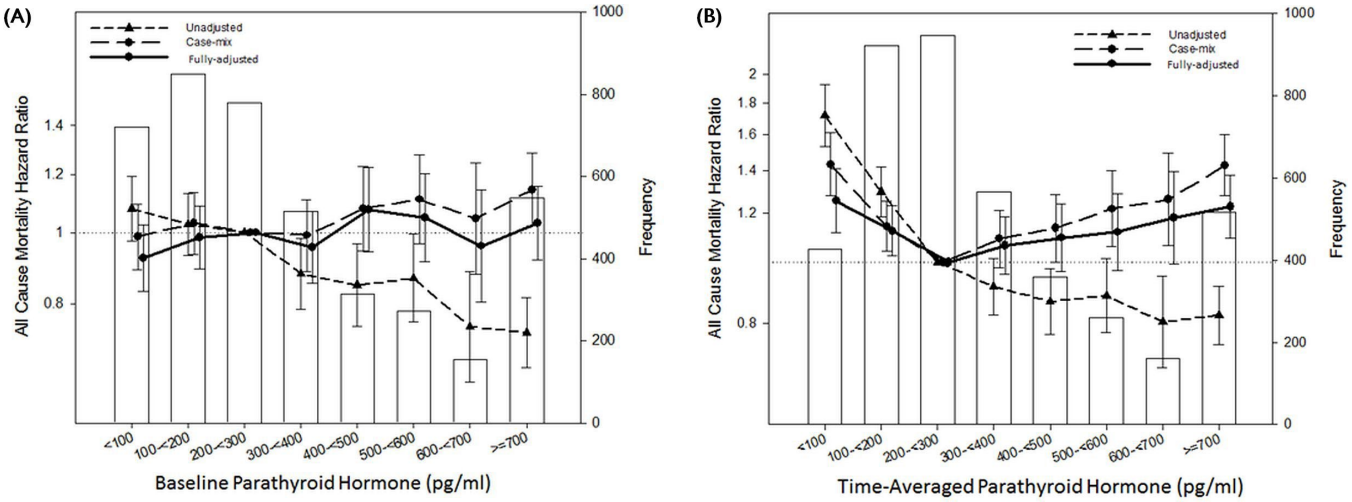

Figure 5 — All-cause mortality hazard ratios for (A) baseline and (B) time-averaged serum parathyroid hormone in 9244 peritoneal dialysis patients. Unadjusted models included the exposure of interest and entry calendar quarter. Case-mix adjusted models included unadjusted model covariates, plus age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin. Fully-adjusted models included case-mix model covariates, plus serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agents.

censoring events. In contrast, our findings suggest that, when examined as a baseline measurement, elevated ALP is associated with increased mortality in PD patients, even within high-normal ranges. Given that several therapeutic interventions (activated vitamin D and calcimimetics, for example) have been shown to lower ALP concentrations, further study is needed to determine if a reduction in serum ALP leads to improved outcomes (46,47).

It is important to note that, in contrast with the analyses of baseline measurements, the analyses using

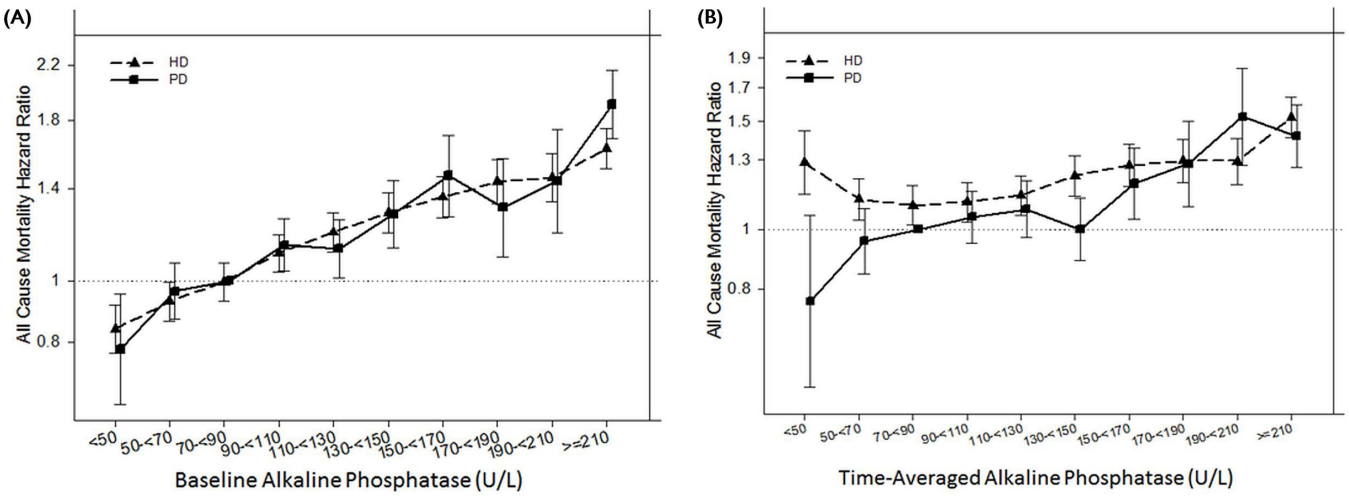

Figure 6 — Comparison of the association between (A) baseline and (B) time-averaged serum alkaline phosphatase (ALP) in 99 323 hemodialysis (HD) patients and 9244 peritoneal dialysis (PD) patients (reference group: PD patients with serum ALP 70 U/L to <90 U/L). Unadjusted models included the exposure of interest and entry calendar quarter. Case-mix adjusted models included unadjusted model covariates, plus age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin. Fully-adjusted models included case-mix model covariates, plus serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agents.

time-averaged measurements did not show a significantly lower risk of death in the lowest ALP categories. Several explanations for this discrepancy are possible. First, time-averaged analyses may better capture the impact of long-term, cumulative ALP exposure. In contrast, baseline ALP might be subject to misclassification and subsequent bias because of single-point-in-time measurements. Thus, findings from the time-averaged analyses might represent the long-term effects of adynamic bone disease in which complications of fracture, hypercalcemia, and cardiovascular calcification may mitigate any survival benefit conferred by low ALP concentrations (48–50). However, given the trend toward lower mortality risk in patients from the lowest time-averaged ALP strata, it is also possible that the analyses were insufficiently powered because the prevalence of PD patients in this category was notably low. Additional studies are needed to clarify the prognostic implications of low ALP in PD patients.

In the present study, we also observed a U-shaped association between time-averaged PTH and mortality in PD patients. In studies of HD patients, high PTH has been associated with increased death risk, presumably because of effects on vascular calcification (2,8,51,52). Furthermore, studies using serial measurements have also suggested that low PTH is associated with increased mortality (8). In addition to adynamic bone disease, risk factors for low PTH (advanced age, white race, high calcium load, protein–energy wasting) and their potential sequelae (withholding of activated vitamin D and calcimimetics) might serve as links between low PTH and mortality (20). Few prior studies have examined mortality-predictability using PTH exclusively in PD patients, and the available results are mixed. In two small studies that used different PTH cut-offs, neither low nor high PTH was associated with mortality (53). In contrast, low PTH concentrations (<65 pg/mL and 65 – 199 pg/mL) compared with concentrations greater than 200 pg/mL were associated with increased death risk in one study of PD patients (53,54). However, for PTH concentrations exceeding 200 pg/mL, a distinction was not made between concentrations of 300 pg/mL or less and concentrations greater than 300 pg/mL, and serial measurements were not considered. To address that uncertainty, we examined baseline and time-averaged PTH with finer granularity. In baseline analyses, we did not observe a significant association with death risk, but in time-averaged analyses, a U-shaped association emerged.

Early studies suggested that, compared with their HD counterparts, PD patients have a disproportionately higher prevalence of low bone turnover, but those investigations were largely conducted before adoption of lower-calcium PD solutions (55). For that reason, we compared the distribution of and mortality-predictability for bone turnover markers according to dialysis modality. More than 60% of PD and HD patients manifested ALP concentrations consistent with normal-to-low bone

TABLE 7
Hazard Ratios (HRs) for All-Cause Mortality by Baseline and Time-Averaged Serum Alkaline Phosphatase (ALP) and Parathyroid Hormone (PTH) in 9244 Peritoneal Dialysis and 99 323 Hemodialysis Patients[a]

Serum concentration group	Baseline concentration				Time-averaged concentration			
	Peritoneal dialysis		Hemodialysis		Peritoneal dialysis		Hemodialysis	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ALP (U/L)								
<50	0.78	0.64 to 0.95	0.84	0.77 to 0.92	0.76	0.55 to 1.05	1.28	1.14 to 1.45
50 to <70	0.96	0.87 to 1.07	0.93	0.86 to 1.00	0.96	0.85 to 1.08	1.12	1.04 to 1.21
70 to <90	Ref		1.00	0.93 to 1.07	Ref		1.09	1.02 to 1.18
90 to <110	1.14	1.04 to 1.25	1.11	1.03 to 1.18	1.05	0.95 to 1.16	1.11	1.03 to 1.19
110 to <130	1.13	1.01 to 1.25	1.19	1.11 to 1.28	1.08	0.97 to 1.20	1.14	1.06 to 1.22
130 to <150	1.28	1.13 to 1.44	1.28	1.19 to 1.38	1.00	0.89 to 1.12	1.22	1.13 to 1.32
150 to <170	1.47	1.27 to 1.70	1.36	1.26 to 1.47	1.19	1.04 to 1.36	1.27	1.18 to 1.38
170 to <190	1.31	1.09 to 1.57	1.44	1.32 to 1.56	1.28	1.09 to 1.50	1.29	1.19 to 1.40
190 to <210	1.44	1.19 to 1.74	1.46	1.34 to 1.59	1.53	1.27 to 1.83	1.29	1.18 to 1.41
≥210	1.91	1.68 to 2.16	1.62	1.51 to 1.74	1.42	1.26 to 1.60	1.52	1.41 to 1.64
PTH (pg/mL)								
<100	0.91	0.82 to 1.00	0.90	0.84 to 0.97	1.23	1.10 to 1.38	1.31	1.22 to 1.41
100 to <200	0.99	0.90 to 1.09	0.92	0.86 to 0.99	1.10	1.01 to 1.21	1.14	1.07 to 1.22
200 to <300	Ref		0.92	0.86 to 0.99	Ref		1.07	1.00 to 1.15
300 to <400	0.95	0.85 to 1.06	0.97	0.90 to 1.04	1.04	0.94 to 1.16	1.11	1.03 to 1.18
400 to <500	1.05	0.92 to 1.19	1.04	0.96 to 1.12	1.06	0.94 to 1.20	1.22	1.14 to 1.31
500 to <600	1.05	0.92 to 1.21	1.05	0.96 to 1.13	1.12	0.97 to 1.28	1.18	1.10 to 1.28
600 to <700	0.94	0.79 to 1.12	1.11	1.02 to 1.21	1.13	0.96 to 1.34	1.30	1.20 to 1.41
≥700	1.04	0.93 to 1.16	1.21	1.12 to 1.31	1.21	1.08 to 1.34	1.46	1.36 to 1.57

CI = confidence interval.

[a] Models were adjusted for entry calendar quarter, age, sex, race or ethnicity, diabetes, congestive heart failure, arteriosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, ferritin, serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agent.

turnover. However, in contrast with earlier data, PD patients had higher odds of having an increased PTH concentration, even after accounting for case-mix and laboratory differences. The disproportionate risk of high bone turnover disease in PD patients compared with HD patients might relate to losses of vitamin D in peritoneal effluent and poor adherence to oral vitamin D therapy, but further study is needed (29).

When comparing the mortality-predictability for time-averaged ALP in HD and PD patients (using PD patients with normal concentrations as the reference group), PD patients experienced increased mortality at higher ALP concentrations, but HD patients experienced increased mortality at all ALP concentrations, particularly in the lowest and highest strata. Similarly, when HD patients were compared with PD patients having normal PTH levels, a U-shaped association was observed between time-averaged PTH and mortality in PD patients, but HD patients experienced increased mortality at all PTH concentrations, especially the lowest and highest categories. Despite extensive adjustment for covariates, residual confounding on the basis of comorbidity status and therapeutic management of PD patients compared with HD patients might yet remain; nevertheless, the data suggest that ALP and PTH derangements have negative prognostic implications in PD and HD patients alike.

Our study has several strengths, including its contemporary timeframe, a large sample of PD and HD patients, uniform laboratory measurements conducted in a single facility, extended follow-up, and extensive measurement and adjustment for confounders. Yet several limitations bear mention. First, we are unable to confirm that elevated ALP measurements originate from a skeletal source or that CKD-MBD pathways underlie the ALP–mortality association. However, analyses adjusted for elevations in a liver enzyme as a possible confounder did not change

TABLE 8
Hazard Ratios for All-Cause Mortality by Baseline and Time-Averaged Serum Alkaline Phosphatase in 9244 Peritoneal Dialysis and 99 323 Hemodialysis Patients with Additional Adjustment for Serum Aspartate Aminotransferase

Serum ALP concentration (U/L)	Baseline concentration				Time-averaged concentration			
	Peritoneal dialysis		Hemodialysis		Peritoneal dialysis		Hemodialysis	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<50	0.78	0.64 to 0.95	0.85	0.77 to 0.92	0.77	0.56 to 1.06	1.28	1.14 to 1.45
50 to <70	0.96	0.87 to 1.07	0.94	0.87 to 1.00	0.96	0.85 to 1.09	1.12	1.03 to 1.21
70 to <90	Reference		1.00	0.94 to 1.08	Reference		1.09	1.01 to 1.17
90 to <110	1.14	1.04 to 1.25	1.11	1.04 to 1.19	1.05	0.95 to 1.15	1.10	1.02 to 1.18
110 to <130	1.12	1.01 to 1.25	1.20	1.12 to 1.29	1.07	0.96 to 1.19	1.12	1.04 to 1.21
130 to <150	1.27	1.13 to 1.44	1.29	1.20 to 1.39	0.98	0.87 to 1.10	1.20	1.11 to 1.30
150 to <170	1.47	1.26 to 1.70	1.36	1.26 to 1.47	1.17	1.02 to 1.34	1.24	1.15 to 1.35
170 to <190	1.30	1.08 to 1.56	1.43	1.32 to 1.56	1.25	1.06 to 1.47	1.26	1.16 to 1.37
190 to <210	1.41	1.16 to 1.71	1.45	1.33 to 1.58	1.50	1.25 to 1.80	1.24	1.14 to 1.36
≥210	1.86	1.65 to 2.11	1.60	1.49 to 1.73	1.36	1.21 to 1.53	1.45	1.34 to 1.56

CI = confidence interval.

[a] Models included serum alkaline phosphatase, entry calendar quarter, age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, serum albumin, ferritin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, weekly dose of erythropoiesis-stimulating agent, and serum aspartate aminotransferase.

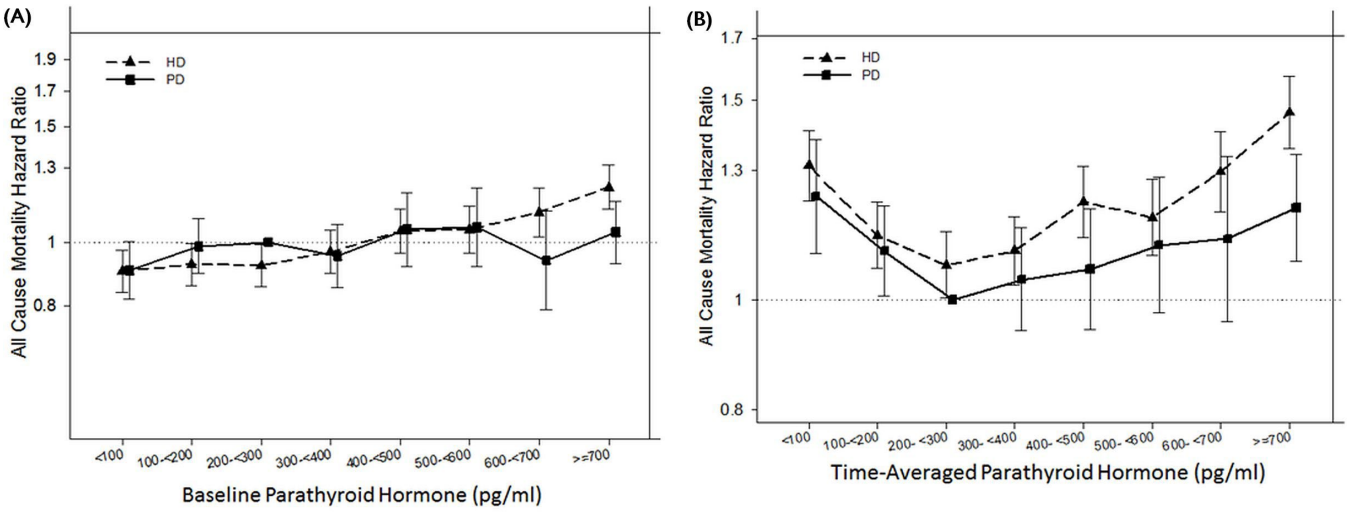

Figure 7 — Comparison of the association between (A) baseline and (B) time-averaged serum parathyroid hormone concentrations in 99 323 hemodialysis (HD) patients and 9244 peritoneal dialysis (PD) patients (reference group: PD patients with parathyroid hormone 200 to <300 pg/mL). Unadjusted models included the exposure of interest and entry calendar quarter. Case-mix adjusted models included unadjusted model covariates, plus age, sex, race or ethnicity, diabetes, congestive heart failure, atherosclerotic heart disease, peripheral vascular disease, other cardiac disease, active tobacco use, dialysis vintage, primary insurance, marital status, body mass index, and ferritin. Fully-adjusted models included case-mix model covariates, plus serum albumin, total iron binding capacity, bicarbonate, creatinine, white blood cell count, lymphocyte percentage, normalized protein catabolic rate, calcium, phosphorus, hemoglobin, and weekly dose of erythropoiesis-stimulating agents.

the results. Second, because of data limitations, we did not account for medications (vitamin D, calcimimetics) or biochemical markers (25-hydroxyvitamin D, fibroblast growth factor 23) that might be associated with ALP and PTH, and we cannot exclude the possibility of residual confounding on that basis (56). Third, we did not account

for changes in dialysis modality over time (that is, transition from PD to HD), which might also have contributed to residual confounding. Fourth, excluded patients differed from those who were included, which may have biased the results. Lastly, as with all observational studies, our findings do not prove that the associations of ALP and PTH with mortality are causal.

CONCLUSIONS

Our findings suggest that elevated ALP and both high and low PTH are associated with increased mortality in PD patients. Given the biologic plausibility of an ALP–cardiovascular disease link, the consistency of epidemiologic data across heterogeneous populations, ease of availability, and ability to lower ALP with medications, ALP might be a promising tool for CKD-MBD management in PD patients. Further studies are now needed to confirm our findings, elucidate underlying mechanisms, and determine if correction of ALP and PTH to target ranges improves outcome in PD patients.

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DISCLOSURES

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REFERENCES

1. Chiu YW, Mehrotra R. Can we reduce the cardiovascular risk in peritoneal dialysis patients? *Indian J Nephrol* 2010; 20:59–67.
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; 15:2208–18.
3. Kidney Disease | Improving Global Outcomes (KDIGO) CKD–MBD Work Group. 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):S1–130.
4. Beddhu S, Baird B, Ma X, Cheung AK, Greene T. Serum alkaline phosphatase and mortality in hemodialysis patients. *Clin Nephrol* 2010; 74:91–6.
5. Beddhu S, Ma X, Baird B, Cheung AK, Greene T. Serum alkaline phosphatase and mortality in African Americans with chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4:1805–10.
6. Blayney MJ, Pisoni RL, Bragg–Gresham JL, Bommer J, Piera L, Saito A, *et al.* High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. *Kidney Int* 2008; 74:655–63.
7. Fahrleitner–Pammer A, Herberth J, Browning SR, Obermayer–Pietsch B, Wirnsberger G, Holzer H, *et al.* Bone markers predict cardiovascular events in chronic kidney disease. *J Bone Miner Res* 2008; 23:1850–8.
8. Kalantar–Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; 70:771–80.
9. Kalantar–Zadeh K, Miller JE, Kovesdy CP, Mehrotra R, Lukowsky LR, Streja E, *et al.* Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *J Bone Miner Res* 2010; 25:2724–34.
10. Kovesdy CP, Ureche V, Lu JL, Kalantar–Zadeh K. Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD. *Nephrol Dial Transplant* 2010; 25:3003–11.
11. Regidor DL, Kovesdy CP, Mehrotra R, Rambod M, Jing J, McAllister CJ, *et al.* Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. *J Am Soc Nephrol* 2008; 19:2193–203.
12. Shantouf R, Kovesdy CP, Kim Y, Ahmadi N, Luna A, Luna C, *et al.* Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients. *Clin J Am Soc Nephrol* 2009; 4:1106–14.
13. Shastri S, Tangri N, Tighiouart H, Beck GJ, Vlagopoulos P, Ornt D, *et al.* Predictors of sudden cardiac death: a competing risk approach in the hemodialysis study. *Clin J Am Soc Nephrol* 2012; 7:123–30.
14. Sigrist MK, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2:1241–8.
15. Garrett G, Sardiwal S, Lamb EJ, Goldsmith DJ. PTH—a particularly tricky hormone: why measure it at all in kidney patients? *Clin J Am Soc Nephrol* 2013; 8:299–312.
16. Goldsmith DJ. Rebuttal: the case for routine parathyroid

hormone monitoring. *Clin J Am Soc Nephrol* 2013; 8:319–20.
17. Sprague SM, Moe SM. Rebuttal: PTH—a particularly tricky hormone: why measure it at all in kidney patients? *Clin J Am Soc Nephrol* 2013; 8:321.
18. Schoppet M, Shanahan CM. Role for alkaline phosphatase as an inducer of vascular calcification in renal failure? *Kidney Int* 2008; 73:989–91.
19. Cantor T. Parathyroid hormone assay drift: an unappreciated problem in dialysis patient management. *Semin Dial* 2005; 18:359–64.
20. Kalantar–Zadeh K, Shah A, Duong U, Hechter RC, Dukkipati R, Kovesdy CP. Kidney bone disease and mortality in CKD: revisiting the role of vitamin D, calcimimetics, alkaline phosphatase, and minerals. *Kidney Int Suppl* 2010; (117):S10–21.
21. Martin KJ, Juppner H, Sherrard DJ, Goodman WG, Kaplan MR, Nassar G, *et al*. First- and second-generation immunometric PTH assays during treatment of hyperparathyroidism with cinacalcet HCl. *Kidney Int* 2005; 68:1236–43.
22. Salusky IB, Juppner H. New PTH assays and renal osteodystrophy. *Pediatr Nephrol* 2004; 19:709–13.
23. Urena P, Hruby M, Ferreira A, Ang KS, de Vernejoul MC. Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. *J Am Soc Nephrol* 1996; 7:506–12.
24. Lomashvili KA, Cobbs S, Hennigar RA, Hardcastle KI, O'Neill WC. Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. *J Am Soc Nephrol* 2004; 15:1392–401.
25. Lomashvili KA, Garg P, Narisawa S, Millan JL, O'Neill WC. Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. *Kidney Int* 2008; 73:1024–30.
26. Giachelli CM. Vascular calcification mechanisms. *J Am Soc Nephrol* 2004; 15:2959–64.
27. Shantouf RS, Budoff MJ, Ahmadi N, Ghaffari A, Flores F, Gopal A, *et al*. Total and individual coronary artery calcium scores as independent predictors of mortality in hemodialysis patients. *Am J Nephrol* 2010; 31:419–25.
28. Brunese L, Romeo A, Iorio S, Napolitano G, Fucili S, Biondi B, *et al*. A new marker for diagnosis of thyroid papillary cancer: B-flow twinkling sign. *J Ultrasound Med* 2008; 27:1187–94.
29. Shah N, Bernardini J, Piraino B. Prevalence and correction of 25(OH) vitamin D deficiency in peritoneal dialysis patients. *Perit Dial Int* 2005; 25:362–6.
30. Torlen K, Kalantar–Zadeh K, Molnar MZ, Vashistha T, Mehrotra R. Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. *Clin J Am Soc Nephrol* 2012; 7:1272–84.
31. Nussbaum SR, Zahradnik RJ, Lavigne JR, Brennan GL, Nozawa–Ung K, Kim LY, *et al*. Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. *Clin Chem* 1987; 33:1364–7.
32. Molnar MZ, Kovesdy CP, Mucsi I, Salusky IB, Kalantar–Zadeh K. Association of pre-kidney transplant markers of mineral and bone disorder with post-transplant outcomes. *Clin J Am Soc Nephrol* 2012; 7:1859–71.
33. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42(Suppl 3):S1–201.
34. Warner EA, Herold AH. Interpreting laboratory tests. In: Rakel RE, Rakel DP, eds. *Textbook of Family Medicine*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2011: 176–204.
35. Fadini GP, Pauletto P, Avogaro A, Rattazzi M. The good and the bad in the link between insulin resistance and vascular calcification. *Atherosclerosis* 2007; 193:241–4.
36. Reslerova M, Moe SM. Vascular calcification in dialysis patients: pathogenesis and consequences. *Am J Kidney Dis* 2003; 41(Suppl 1):S96–9.
37. Narisawa S, Harmey D, Yadav MC, O'Neill WC, Hoylaerts MF, Millan JL. Novel inhibitors of alkaline phosphatase suppress vascular smooth muscle cell calcification. *J Bone Miner Res* 2007; 22:1700–10.
38. Damera S, Raphael KL, Baird BC, Cheung AK, Greene T, Beddhu S. Serum alkaline phosphatase levels associate with elevated serum C-reactive protein in chronic kidney disease. *Kidney Int* 2011; 79:228–33.
39. Kovesdy CP, Kalantar–Zadeh K. Vitamin D receptor activation and survival in chronic kidney disease. *Kidney Int* 2008; 73:1355–63.
40. Filipowicz R, Greene T, Wei G, Cheung AK, Raphael KL, Baird BC, *et al*. Associations of serum skeletal alkaline phosphatase with elevated C-reactive protein and mortality. *Clin J Am Soc Nephrol* 2013; 8:26–32.
41. Yeoh LY, Sivaraman P. Factors that might adversely affect short-term survival of patients starting peritoneal dialysis and use of those factors to predict outcome—a single-center experience. *Perit Dial Int* 2003; 23(Suppl 2):S116–20.
42. Abramowitz M, Muntner P, Coco M, Southern W, Lotwin I, Hostetter TH, *et al*. Serum alkaline phosphatase and phosphate and risk of mortality and hospitalization. *Clin J Am Soc Nephrol* 2010; 5:1064–71.
43. Drechsler C, Verduijn M, Pilz S, Krediet RT, Dekker FW, Wanner C, *et al*. on behalf of the NECOSAD Study Group. Bone alkaline phosphatase and mortality in dialysis patients. *Clin J Am Soc Nephrol* 2011; 6:1752–9.
44. Krishnamurthy VR, Baird BC, Wei G, Greene T, Raphael K, Beddhu S. Associations of serum alkaline phosphatase with metabolic syndrome and mortality. *Am J Med* 2011; 124:566.e1–7.
45. Tonelli M, Curhan G, Pfeffer M, Sacks F, Thadhani R, Melamed ML, *et al*. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. *Circulation* 2009; 120:1784–92.
46. Belozeroff V, Goodman WG, Ren L, Kalantar–Zadeh K. Cinacalcet lowers serum alkaline phosphatase in maintenance hemodialysis patients. *Clin J Am Soc Nephrol* 2009; 4:673–9.

47. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2009; (4):CD008175.
48. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis* 2000; 36:1115–21.
49. London GM, Marchais SJ, Guerin AP, Boutouyrie P, Metivier F, de Vernejoul MC. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* 2008; 19:1827–35.
50. Malluche HH, Monier–Faugere MC. Risk of adynamic bone disease in dialyzed patients. *Kidney Int Suppl* 1992; 38:S62–7.
51. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS Waves 1, 3, and 4 Study. *J Am Soc Nephrol* 2005; 16:1788–93.
52. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, *et al.* Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2005; 67:1179–87.
53. Noordzij M, Korevaar JC, Bos WJ, Boeschoten EW, Dekker FW, Bossuyt PM, *et al.* Mineral metabolism and cardiovascular morbidity and mortality risk: peritoneal dialysis patients compared with haemodialysis patients. *Nephrol Dial Transplant* 2006; 21:2513–20.
54. Dimkovic NB, Bargman J, Vas S, Oreopoulos DG. Normal or low initial PTH levels are not a predictor of morbidity/mortality in patients undergoing chronic peritoneal dialysis. *Perit Dial Int* 2002; 22:204–10.
55. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, *et al.* The spectrum of bone disease in end-stage renal failure—an evolving disorder. *Kidney Int* 1993; 43:436–42.
56. Gutierrez OM, Mannstadt M, Isakova T, Rauh–Hain JA, Tamez H, Shah A, *et al.* Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; 359:584–92.