High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death

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We evaluated risks associated with elevated alkaline phosphatase in hemodialysis patients using longitudinal data from the Dialysis Outcomes and Practice Patterns Study, a prospective observational study of hemodialysis patients in 12 countries. Alkaline phosphatase levels were normalized by the upper limit of the laboratory-reported reference range. Cause-specific hospitalization and mortality risks were evaluated using Cox proportional hazards models, stratified by region and adjusted for phosphorus, calcium, albumin, parathyroid hormone, case mix, and numerous comorbidities. The odds of high normalized alkaline phosphatase were increased twofold in the United States in comparison to Japan. Elevations of normalized alkaline phosphatase were significantly associated with several comorbid conditions, increased fractures, parathyroidectomy, risk of hospitalization due to major adverse cardiac events, higher all-cause cardiovascular, and infection-related mortality risk. Our results also show that elevated serum normalized alkaline phosphatase was associated with higher risks of hospitalization and death in hemodialysis patients, independent of calcium, phosphorus, and parathyroid hormone levels.

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Altered patterns of mineral metabolism, including alkaline phosphatase (AP), are often observed in end-stage renal disease (ESRD) patients on hemodialysis (HD) therapy. In HD patients, elevated levels of serum AP are associated with secondary hyperparathyroidism (SHPT),[1,2] renal osteodystrophy,[3,4] cardiac failure, diastolic dysfunction,[5] and cardiovascular disease (CVD).[6] Serum total AP commonly includes isoenzymes from bones and liver, as well as kidneys, intestines,[7] or leukocytes.[8] Although correlations of AP isoenzyme elevations to elevated parathyroid hormone (PTH) have been documented, few studies have examined the risks associated with elevated AP in HD patients. Notably, Kalantar-Zadeh *et al.*[9] demonstrated an increased risk of all-cause mortality associated with higher baseline and time-varying AP levels in HD patients, without including adjustments for elevated serum phosphorus and calcium levels, which have been associated with higher mortality risk.[10]

The present study was based on the hypothesis that elevated AP levels are an independent marker of increased mortality risk in HD patients. We aimed to identify the factors and risks associated with elevated AP using longitudinal data from the Dialysis Outcomes and Practice Patterns Study (DOPPS). The international nature and large sample size of DOPPS allowed comparison of AP levels in HD patients across 12 countries and evaluation of over 30 predictors of elevated AP. Detailed information about cause of hospitalization and death collected by DOPPS enabled us to assess the relationship between AP levels with cause-specific morbidity and mortality.

RESULTS

Subject eligibility

Representing all 12 countries, 198 DOPPS I and 248 DOPPS II facilities met the inclusion criterion for these analyses (Table 1). From these facilities, baseline normalized AP (nAP) data were determined for 14,643 patients (DOPPS I and II), and longitudinal data for 7550 patients (DOPPS I).

Table 1 | Descriptive statistics of baseline patient normalized AP values countrywise: DOPPS II

Country (*n* facilities)	Baseline data from a prevalent cross-section of DOPPS II patients			
	n patients	Country mean nAP (± s.d.)	Country median nAP	Patient nAP > 1.0 (%)
Japan (57)	1727	0.77 (0.48)	0.67	17.4*
US (57)	1671	0.99 (0.81)	0.81	32.8*
Spain (18)	557	0.89 (0.70)	0.74	24.6
Belgium (17)	466	0.85 (0.51)	0.71	26.5
Australia–New Zealand (19)	466	0.96 (1.39)	0.75	26.6
Canada (14)	407	0.89 (0.61)	0.75	24.9
Germany (14)	403	1.04 (4.94)	0.67	18.7*
France (15)	370	1.28 (5.31)	0.68	23.0
Italy (12)	351	1.05 (1.09)	0.82	32.9*
United Kingdom (12)	329	0.77 (0.50)	0.66	22.5
Sweden (13)	330	0.89 (0.96)	0.63	22.0

DOPPS, Dialysis Outcomes and Practice Patterns Study; nAP, normalized alkaline phosphatase.
The percentage of patients with nAP > 1.0 from each country was compared to the overall mean percentage of patients with nAP > 1.0 with adjustments made for facility-clustering effects.
*$P < 0.05$.

Patient demographics

In DOPPS II, country median nAP values varied from 0.63 in Sweden to 0.81–0.82 in the United States of America (US) and Italy (Table 1). Compared to the overall mean percentage, the United States of America and Italy had a significantly larger percentage of patients with nAP > 1.0 (32.8 and 32.9%), whereas Japan and Germany had a significantly lower percentage (17.4 and 18.7%).

Table 2 shows significant ($P < 0.05$) differences in the baseline case-mix and comorbid characteristics between mildly or markedly elevated versus normal nAP categories. The missing nAP category had a significantly ($P < 0.05$) higher mean BMI (body mass index) and percentage of black patients, and a significantly lower percentage of patients with cancer, hypertension, hepatitis C, fistula use, or vitamin D treatment than the non-missing category. Among a prevalent cross-section of DOPPS II patients from countries with sevelamer use ($n = 1414$), 23% were prescribed sevelamer, 61% calcium-based phosphate binders, and 3% other phosphate binders, whereas 12% were not prescribed any phosphate binder (data not shown).

Predictors of elevated nAP

Significantly ($P < 0.05$) higher odds of mildly elevated nAP values ($1.0 < \text{nAP} \leqslant 1.4$ versus $\leqslant 1.0$) were predicted by lower serum phosphorus, calcium, albumin, or higher PTH (Table 3), and were also associated with lower BMI, hepatitis C, ascites, diabetes, CVD other than coronary artery disease or congestive heart failure, psychiatric disorder, or no prior parathyroidectomy (PTx) or hypertension. There was a strong relationship between the odds of mildly elevated nAP and time since ESRD onset, with patients nearly twice as likely to display mildly elevated nAP if living with ESRD for more than 9 years compared with patients living with ESRD for less than 3 years (data not shown).

In addition to predictors of mildly elevated nAP (except a prior PTx), the odds of markedly elevated nAP (> 1.4 versus $\leqslant 1.0$) were significantly higher in 18- to 44-year-old males, and in patients with coronary artery disease, no cerebrovascular disease, gastrointestinal (GI) bleeding, peripheral arterial disease, and recurrent cellulitis or gangrene. In a sub-analysis of DOPPS II patients, C-reactive protein was a significant predictor of markedly (adjusted odds ratio (AOR) = 5.16; $P = 0.02$) but not mildly (AOR = 1.57; $P = 0.4$) elevated nAP versus normal nAP. Transferrin was not a significant predictor of mildly or markedly elevated nAP (AOR = 1.0 and 1.0; $P = 0.2$ and 0.3, respectively). When history of alcohol abuse in the past 12 months (a component of the psychiatric disease comorbid classification) was included in a sensitivity model without psychiatric disease as a covariate, it was significantly predictive of higher odds of mildly but not markedly elevated nAP (AOR = 1.19, $P = 0.03$ and AOR = 1.01, $P = 0.9$, respectively).

Women aged 45–59 years had significantly higher odds of mildly or markedly elevated nAP compared with women aged 18–44 years. A sub-analysis of women aged 45–49 and 50–59 years showed that higher odds of elevated nAP were consistent throughout this age range (data not shown). The odds of markedly elevated nAP were lower for all categories of males aged $\geqslant 45$ years, compared with men aged < 45 years. In an independent linear regression model with age and sex modeled as covariates, male HD patients had significantly ($P < 0.0001$) lower odds of mildly or markedly elevated nAP values (AOR = 0.78 and 0.67, respectively) compared with female patients.

The adjusted odds of mildly elevated nAP levels were significantly lower for Japan or Europe versus North America ($P < 0.0001$ and $P = 0.04$, respectively). Without adjustment for hepatitis C and other comorbidities, Japan had consistently lower odds OR of mildly or markedly elevated AP than North America (OR = 0.58 and 0.4, respectively; both $P < 0.0001$). Europe (compared with North America) displayed a significantly lower unadjusted OR of mildly or markedly elevated nAP (OR = 0.73, $P < 0.0001$ and OR = 0.69, $P = 0.001$, respectively).

Among DOPPS II countries where sevelamer was available, baseline use of sevelamer (compared with calcium-based