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Impact of the serum bone-specific alkaline phosphatase level at the initiation of hemodialysis therapy for end-stage renal disease on cardiovascular events

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ABSTRACT

Background: Patients with end-stage renal disease (ESRD) have high rates of hospitalization for cardiovascular (CV) events and short-term mortality after the initiation of hemodialysis (HD) therapy. To improve outcomes, it is important to identify predictive laboratory markers. We investigated whether the serum bone-specific alkaline phosphatase (BAP) level at the initiation of HD therapy for ESRD was associated with adverse events.
Methods: This was a retrospective cohort study of 47 ESRD outpatients who were referred to our clinic for HD. The serum BAP level was measured within 1 month after the initiation of HD. Patients were divided into high-BAP and low-BAP groups according to the median serum BAP level (24.6 U/L). The impact of the serum BAP level on CV events (coronary artery disease, peripheral arterial disease, cerebrovascular disease, other CV events including aortic dissection, and mortality) was investigated.
Results: During a median follow-up period of 72 months, CV events occurred in 14 patients (29.8%). Kaplan–Meier analysis showed that the disease-free and overall survival rates were lower in the high-BAP group than in the low-BAP group ($p = 0.003$ and $p = 0.037$, respectively, log-rank test). After adjustment for age, sex, and other confounding factors, Cox proportional hazards analysis found that the high-BAP group had a 5.9-fold higher rate of CV events than the low-BAP group (hazard ratio: 5.89; 95% confidence interval: 1.184–29.309; $p = 0.030$).
Conclusions: The serum BAP level at the initiation of HD therapy for ESRD is a useful non-invasive biomarker for predicting CV events.

1. Introduction

Patients undergoing dialysis have significantly higher rates of hospitalization for cardiovascular (CV), cerebrovascular, and peripheral arterial disease (PAD) than those not undergoing dialysis [1–5]. It is therefore important to identify predictive factors for CV events in patients with end-stage renal disease (ESRD) who are starting dialysis [6,7]. The identification of associations between laboratory markers at the initiation of hemodialysis (HD) and CV events enables risk stratification of patients with ESRD.

ESRD is associated with disorders of bone metabolism such as chronic kidney disease (CKD)–mineral and bone disorder (MBD) [8]. CKD–MBD is associated with the development of vascular calcification, which contributes to the morbidity and mortality of dialysis patients [9,10]. The abnormalities of mineral and bone metabolism begin prior to the initiation of dialysis, and there is a significant progression of vascular calcification in HD patients compared with CKD stage 4 patients [11,12]. These findings suggest that the preceding abnormalities of mineral and bone metabolism may be associated with CV events in new dialysis patients.

Bone-specific alkaline phosphatase (BAP) is a laboratory marker used to assess mineral and bone metabolism in patients with ESRD [13]. The Kidney Disease: Improving Global Outcomes position statement indicates that the improvement of non-invasive diagnosis of CKD–MBD and associated CV complications is urgently needed to improve outcomes in patients with CKD [8]. However, the relationship

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between the serum BAP level at the initiation of HD and prognosis remains unclear.

The purpose of this retrospective cohort study was to elucidate the value of the serum BAP level at the initiation of HD therapy, which is a direct marker of bone turnover, for predicting adverse CV events in ESRD patients.

2. Methods

2.1. Patients

Eighty-eight patients with ESRD were referred to the Dialysis Unit of Shinjuku Ishikawa Clinic (Shinjuku-ku, Tokyo, Japan) within 1 month after starting HD between 2005 and 2008. The 72 patients who received three dialysis sessions per week were reviewed. Patients with malignancy (n = 2), infectious or inflammatory disease (n = 2), chronic liver disease (n = 1), lower extremity amputation for PAD (n = 2), or no serum BAP level measured within 1 month (n = 18) were excluded. The remaining 47 patients were included in the analysis of the relationship between the serum BAP level at the initiation of HD and CV events. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault equation [14]. Patient characteristics, co-morbid conditions, and medications were recorded from the medical notes and referral form. This retrospective study protocol was approved by the institutional review board of Tokyo Women's Medical University.

2.2. Blood sampling

Blood was taken before dialysis to measure the circulating levels of various markers, including calcium (Ca) and phosphorus. Serum Ca levels were adjusted using the formula [Ca + (4-albumin)]. Serum whole parathyroid hormone (PTH) (1–84) level and BAP level were measured using an IRMA kit (DS Pharma Biomedical, Osaka, Japan) and an EIA kit (Alkphase-B, Metra Biosystems, Mountain View, CA, USA), respectively. The serum BAP level was measured within 1 month after the initiation of HD.

2.3. Assessment of aortic arch calcification (AoAC)

The presence or absence of AoAC on the first posteroanterior chest X-ray after starting HD was assessed. AoAC was defined as any visible calcification, including small spots of calcification, a single thin area of calcification at the aortic knob, one or more areas of thick calcification, or circular calcification at the aortic knob [15].

2.4. Definitions of CV events

CV morbidity and mortality were recorded. CV morbidity included coronary artery disease (CAD), PAD, stroke, intracranial hemorrhage, and other CV events requiring hospitalization. CAD was defined as acute coronary syndrome or percutaneous coronary intervention for stable or unstable angina. PAD was defined as angiographically verified stenosis of the peripheral arteries with cold extremities, numbness, intermittent claudication, or pain at rest. Stroke and intracranial hemorrhage were diagnosed by imaging studies or neurological criteria. Other CV events included aortic dissection. Disease-free survival (DFS) was defined as the time from enrollment to the CV event or death, whichever occurred first. Overall survival (OS) was defined as the time from enrollment to death from any cause. Follow-up data were available for all patients to May 31, 2013.

2.5. Statistical analysis

All variables were tested for a normal distribution using the Shapiro–Wilk test. The data are presented as mean ± SD, or as median and range. The baseline clinical data were compared between groups using the Student's t-test or Mann–Whitney U test. Categorical variables were compared using a chi-square analysis. Because of the lack of a recommended cutoff value for the serum BAP level and its non-normal distribution, patients were dichotomized into a low-BAP group (serum BAP level lower than the median) and a high-BAP group (serum BAP level equal to or higher than the median). The cumulative event-free survival was calculated using the Kaplan–Meier analysis. Differences in DFS and OS between groups were assessed using the log-rank test. The predictors of DFS and OS were identified using the Cox proportional hazards model. The hazard ratio (HR) with 95% confidence interval (CI) was calculated for each factor by Cox univariate analysis. Cox multivariate analyses for DFS and OS were adjusted for age, sex, and the factors found to be significantly associated with outcome on univariate analysis. As the serum alkaline phosphatase (ALP) level has colinearity with the serum BAP level, the ALP level was excluded from the analysis. All p values are two-sided. Differences were considered to be statistically significant at $p < 0.05$. Statistical analyses were performed using IBM SPSS software version 19.0 (IBM, Somers, NY, USA).

3. Results

3.1. Patient characteristics

The baseline characteristics of patients are shown in Table 1. The study group included 47 patients (33 men, 14 women) with a mean age of 56 ± 17 years. The median follow-up period was 72 months (range, 16–96 months). The median serum BAP level was 24.6 U/L (range, 10.8–84.2 U/L). The high-BAP group had a lower proportion of male patients than the low-BAP group. The serum ALP level, whole PTH level, and eGFR were higher in the high-BAP group than in the low-BAP group. The use of anti-hyperparathyroid agents, including phosphate binders and vitamin D therapy, was less frequent in the high-BAP group than in the low-BAP group. AoAC and a history of CAD tended to be more frequent in the high-BAP group than in the

Table 1
Baseline demographic characteristics according to the serum BAP level.

	Lower BAP (BAP < 24.6)	Higher BAP (BAP ≥ 24.6)	p value
Numbers	23	24	
Age (years)	52 ± 15	59 ± 18	0.126
Male (%)	87.0	58.3	0.028
Body mass index (kg/m^2)	23.2 ± 3.3	21.8 ± 3.3	0.192
Blood pressure (mm Hg)			
Systolic	141 ± 22	136 ± 18	0.445
Diastolic	83 ± 13	79 ± 12	0.296
Comorbidity (%)			
Diabetes mellitus	30.4	45.8	0.278
History of CAD	13.0	20.8	0.477
Laboratory values			
Albumin (g/dL)	4.0 ± 0.4	3.9 ± 0.4	0.369
Hemoglobin (g/dL)	9.0 ± 1.2	9.6 ± 1.2	0.126
eGFR (mL/min per 1.73 m^2)	5.5 ± 1.9	7.4 ± 3.1	0.011
ALP (U/L)	211.1 ± 76.6	287.1 ± 93.2	0.004
Serum calcium (mg/dL)	8.1 ± 0.9	8.0 ± 0.5	0.851
Serum phosphate (mg/dL)	6.0 ± 1.3	5.2 ± 1.7	0.086
Whole PTH (pg/dL)	99.8 ± 56.1	173.2 ± 124.9	0.017
Magnesium (mg/dL)	2.4 ± 0.5	2.2 ± 0.6	0.311
Uremic acid (mg/dL)	7.6 ± 1.8	7.3 ± 1.6	0.559
Presence of AoAC (%)	26.1	41.7	0.260
Medications (%)			
ACE inhibitor or ARB use	82.6	78.3	0.710
β-Blocker use	30.4	29.2	0.924
Anti-HPT drug use	91.3	62.5	0.020
Statin use	13	17.4	0.681

Values are mean (±SD) or percentage. BAP, bone-specific alkaline phosphatase; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate based on the Modification of Diet in Renal Disease formula; ALP, alkaline phosphatase; PTH, parathyroid hormone; AoAC, aortic arch calcification; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HPT, hyperparathyroid.

low-BAP group. There were no significant differences in age, body mass index, systolic or diastolic blood pressure, prevalence of diabetes mellitus, albumin level, hemoglobin level, calcium level, phosphorus level, magnesium level, uremic acid level, use of antihypertensive agents, use of β-blockers, or use of statins between the two groups at baseline.

3.2. Patient outcomes

During the follow-up period, 11 CV events and 8 deaths occurred in 14 patients (Table 2). Among the patients who died, two had coronary artery events, one had an intracranial hemorrhage, and two had peripheral arterial events. The most common cause of CV events was CAD (45.5%), followed by stroke or intracranial hemorrhage (27.3%). Eight patients (17.0%) died by the end of May 2013.

3.3. Impact of the serum BAP level on CV events and mortality

Kaplan–Meier curves for DFS and OS, stratified according to the median serum BAP level, are shown in Fig. 1. DFS was worse in the high-BAP group than in the low-BAP group ($p = 0.003$, log-rank test). CV events tended to occur in the early years after the initiation of HD. OS was also worse in the high-BAP group than in the low-BAP group ($p = 0.037$, log-rank test). Death tended to occur several years after the initiation of HD. The difference between the time of the first non-fatal CV event and the time of death was 3.7 ± 1.7 years. Receiver operating characteristic curve analysis showed that the optimal cutoff value of the serum BAP level for predicting CV events was 24.2 U/L. This cutoff value had high sensitivity (92.9%) and moderate specificity (63.6%). The optimal cutoff value of the serum BAP level for predicting overall death was 30.9 U/L. This cutoff value had moderate sensitivity (62.5%) and moderate specificity (76.9%).

3.4. Univariate and multivariate analyses for CV events and mortality

Univariate and multivariate Cox proportional hazards analyses were performed to identify the factors predicting CV events (Table 3). Univariate analyses found that age, eGFR, and a high serum BAP level were associated with CV events. Multivariate analysis found that patients with a high serum BAP level had a 5.9-fold increased risk of CV events compared with patients with a low serum BAP level (HR: 5.89; 95% CI: 1.184–29.309; $p = 0.030$). After adjustment for age, sex, and history of CAD, OS tended to be worse in the high-BAP group than in the low-BAP group (HR: 3.24; 95% CI: 0.314–33.405; $p = 0.324$), but this difference was not significant.

Table 2
Summary of outcomes for analysis of DFS and OS.

Case	Gender	Age	DFS	OS
1	F	72	ACS	Death
2	F	75	ACS	
3	M	80	ACS	
4	M	71	Underwent PCI	
5	M	59	Underwent PCI	Death
6	M	52	Stroke	
7	M	45	Stroke	
8	M	80	Intracranial hemorrhage	Death
9	M	71	PAD	Death
10	F	72	PAD	Death
11	M	29	Aortic dissection (Stanford A)	
12	M	72	Cardiac sudden death	Death
13	M	73	Death (malignancy)	Death
14	F	54	Death (malignancy)	Death

DFS, disease-free survival; OS, overall survival; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease.

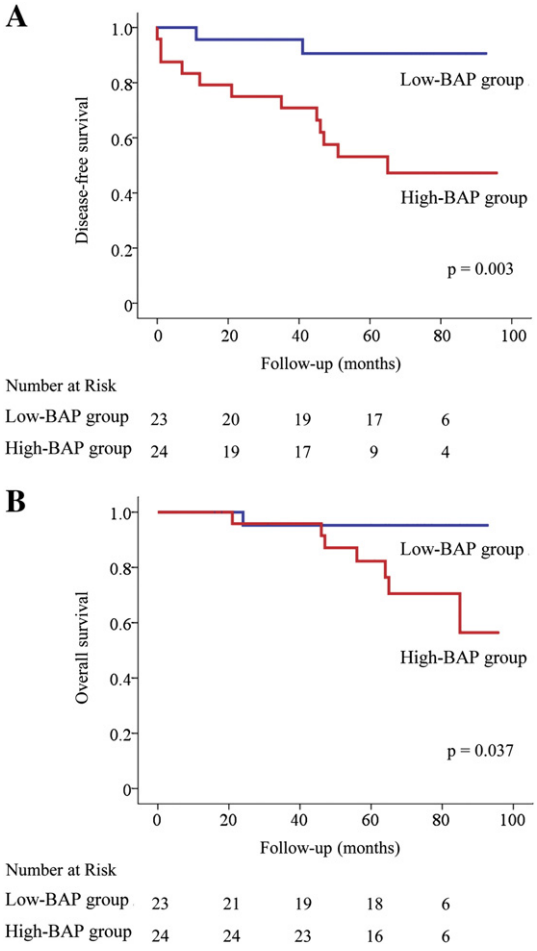

Fig. 1. Kaplan–Meier analyses of (A) disease-free survival and (B) overall survival. Patients were divided into two groups according to the median serum BAP level. The disease-free and overall survival rates were lower in the high-BAP group than in the low-BAP group. Patients who underwent renal transplantation were censored at the time of transplantation for both Kaplan–Meier analyses. For disease-free survival, patients were censored at the end of the follow-up period if they were alive without CV events. For overall survival, patients were censored at the end of the follow-up period if they were alive.

4. Discussion

The results of this study demonstrate that: (1) a high serum BAP level at the initiation of HD was associated with CV events; (2) a high serum BAP level was an independent risk factor for CV events; (3) CV events were generally observed in the early years after the initiation of HD; and (4) CAD was the leading cause of CV events. The clarification of the prognostic values of non-invasive measurements at the initiation of HD is urgently needed to improve outcomes in patients with ESRD. Data regarding the impact of the serum BAP level at the initiation of HD for ESRD on clinical outcomes are currently lacking. The results of this study provide information on the value of the serum BAP level for predicting CV events in patients starting dialysis.

In this study, we showed that the serum BAP level at the initiation of HD is an important predictive factor for CV events. Our results are consistent with those of previous studies [16,17], which reported that a high serum BAP level was a significant predictor of all-cause death in patients receiving HD. However, previous studies measured the serum BAP level during the maintenance phase of HD therapy, and the findings cannot be extrapolated to ESRD patients starting HD. Furthermore, morbidity and mortality rates have been still high during the early years of dialysis [18]. These findings suggest that the measurement of the serum BAP level should be evaluated at the initiation of dialysis therapy to improve the clinical outcomes for patients starting dialysis.

Table 3
Univariate and multivariate analyses for DFS and OS.

	DFS						OS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value	HR	(95% CI)	p value
Age (years)	1.050	1.004–1.096	0.034	1.044	0.991–1.101	0.107	1.093	1.011–1.181	0.025	1.085	1.005–1.170	0.036
Male gender	0.925	0.290–2.953	0.896	2.307	0.577–9.546	0.249	0.629	0.150–2.643	0.527	1.816	0.405–8.138	0.436
Diabetes mellitus	1.644	0.576–4.691	0.353				3.189	0.721–14.111	0.126			
History of CAD	1.385	0.386–4.975	0.617				4.486	1.000–20.121	0.050	3.261	0.641–16.594	0.155
Presence of AoAC	2.699	0.937–7.774	0.066				2.947	0.699–12.427	0.141			
Use of anti-HPT drugs	0.776	0.243–2.477	0.668				0.510	0.122–2.141	0.358			
eGFR	1.376	1.135–1.668	0.001	1.195	0.966–1.478	0.101	1.127	0.897–1.416	0.306			
Ca × P (mg^2/dL^2)	0.952	0.899–1.008	0.089				0.973	0.916–1.034	0.379			
Whole PTH (pg/mL)	0.998	0.992–1.004	0.542				0.994	0.983–1.005	0.261			
BAP (≥24.6 U/L)	6.916	1.545–30.965	0.011	5.891	1.184–29.309	0.030	6.854	0.841–55.862	0.072	3.238	0.314–33.405	0.324

DFS, disease-free survival; OS, overall survival; CAD, coronary artery disease; AoAC, aortic arch calcification; HPT, hyperparathyroid; eGFR, estimated glomerular filtration rate based on the Modification of Diet in Renal Disease formula; Ca, calcium; P, phosphate; PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase.

In the present study, CV events were more frequent in the high-BAP group than in the low-BAP group, especially during the early years after initiation of HD. These results may have important clinical implications for patients starting HD. First, it has been reported that the risk of adverse events is particularly high during the first 2 years after the initiation of dialysis, and that patients with CAD have a higher risk of death during this time than those without CAD [19,20]. In the present study, a history of CAD tended to be associated with death. Second, patients who undergo coronary revascularization procedures after the initiation of renal replacement therapy have poor long-term survival [21,22]. Third, the 3-year mortality rate after limb revascularization procedures is significantly higher in patients with ESRD than those without ESRD [23]. Finally, Sozio et al. reported that cerebrovascular events occurred 10 times more frequently in patients starting dialysis than in the general population, and that these events had a significant risk of mortality [4]. In the present study, CV events were non-fatal in the early years after the initiation of HD, but the longer-term mortality rate tended to be higher in the high-BAP group than in the low-BAP group, despite the better prognosis of Japanese HD patients relative to those in other countries [24]. The avoidance of revascularization procedures after CV events within a few years after the initiation of HD may result in a reduced risk of overall mortality.

The results of the present study show that CAD was the leading cause of CV events after the initiation of HD. It has been reported that patients with ESRD are already at a very high risk of coronary artery stenosis at the initiation of renal replacement therapy [25]. Furthermore, Kono et al. reported that coronary plaque morphology in patients with HD is correlated with mineral disorders [26]. Our results strengthen the association between the degree of disordered mineral metabolism at the initiation of HD for ESRD and CV events.

BAP is a useful biomarker that reflects both bone turnover and vascular calcification [13,27]. Vascular calcification is one of the major complications of CKD–MBD [7]. In vitro studies found that vascular smooth muscle cells derived from the vascular media can be stimulated to undergo phenotypic transformation into bone-forming osteoblast-like cells [13,28], and that such transformation increases the expression of BAP [29]. Orita et al. reported a correlation between the serum BAP level and the area of calcified lesions in an animal model [30]. Furthermore, arterial media calcification is common in HD patients and is a strong prognostic indicator of all-cause and CV mortality [31,32]. In the present study, vascular calcification on chest X-ray tended to be more frequent in the high-BAP group than in the low-BAP group. In addition, it has been reported that starting dialysis accelerates medial vascular calcification by triggering smooth muscle cell apoptosis [33]. These findings suggest that the initiation of dialysis may promote vascular calcification and lead to CV events independently of the serum BAP level. All the patients in this study received HD, and future studies should evaluate the impact of an elevated serum BAP level with or without starting HD on CV events.

Our results show that intervention for CKD–MBD in stage 5D renal disease might be too late. It has been reported that an elevated serum BAP level in patients with advanced stages of CKD is a risk factor for CV events [34], and it is important to lower the serum BAP level before dialysis. Recent clinical studies reported that the administration of vitamin D analogs in CKD stages 3–4 and dialysis patients reduced the serum BAP level [35,36]. Further studies are needed to determine whether early intervention to lower the serum BAP level prior to dialysis can decrease the rate of CV events.

5. Study limitations

Several limitations of our study should be discussed. First, there was an inherent limitation in the retrospective cohort study design. The study was conducted at a single center, and the sample size was small. Second, we measured the serum BAP level at a single time point, which did not allow us to evaluate the effects of changes in serum BAP level after therapeutic interventions. Finally, we did not perform bone biopsies, and therefore cannot confirm a direct relationship between the serum BAP level and bone status in our population. It has previously been reported that the serum BAP level reflects bone histomorphometry findings, and Urena et al. found that a high serum BAP level predicted histological findings indicating high-turnover bone disease [13,37].

6. Conclusions

The results of this study show that a high serum BAP level at the initiation of dialysis is an independent predictor of CV events. Starting the management of mineral and bone disorders in an earlier CKD stage may reduce the frequency of adverse CV events after the initiation of HD therapy.

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There are no funding sources or conflicts of interest to declare.

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