A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among patients receiving hemodialysis in Japan

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ABSTRACT

Background. Monitoring of serum alkaline phosphatase (ALP) is recommended in the management of chronic kidney disease-mineral and bone disorder (CKD-MBD). However, unlike calcium, phosphate or parathyroid hormone, the relationship between serum ALP and patient outcome receiving hemodialysis (HD) in Japan is unknown. Methods. Baseline data of 185 277 HD patients with duration >90 days (66 ± 12 years, males 61.9%, and median HD duration of 5.8 years) were extracted from a nationwide dialysis registry at the end of 2009 in Japan. Outcomes were then evaluated using the registry at the end of 2010 using a multivariate logistic regression analysis.

Results. During 1-year follow-up, 14 230 (7.9%) patients died of all causes, including 6396 (3.6%) cardiovascular deaths. In addition, 1586 patients (1.0%) were newly diagnosed as hip fractures. All-cause and cardiovascular mortalities and the incidence of hip fracture were higher in line with the increase in baseline serum ALP. On multivariate analysis, patients with the highest ALP quartile had higher all-cause and cardiovascular mortalities and a higher incidence of hip fracture than those with the lowest quartile [odds ratio (OR) 1.46, 95% confidence interval (CI) 1.33–1.60; OR 1.25, 95% CI 1.10–1.42; and OR 1.71, 95% CI 1.33–2.18, respectively].

Conclusions. In this large cohort study, higher serum ALP levels were independently associated not only with mortality but also with the incidence of hip fracture in Japanese HD patients.

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patients. Further study is needed to test whether serum ALP measurements could improve the patient outcomes.

**Keywords:** alkaline phosphatase, cardiovascular disease, chronic kidney disease-mineral and bone disorder, hemodialysis, parathyroid hormone

### INTRODUCTION

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism due to CKD, and it manifests in either one or a combination of the following: (i) abnormalities of calcium, phosphorus, parathyroid hormone (PTH) or vitamin D metabolism; (ii) abnormalities in bone turnover, mineralization, volume, linear growth or strength; (iii) vascular or other soft tissue calcification [1]. The important outcomes caused by this clinical condition are mortality, cardiovascular events and fractures.

We monitored circulating phosphorus, calcium, PTH and alkaline phosphatase (ALP) levels in the management of CKD-MBD. ALP is mainly a biochemical marker of bone turnover, and it is usually used to monitor metabolic bone disease, particularly the management of CKD-MBD [2]. It is well known that a higher serum ALP is associated with increased risks of all-cause and cardiovascular mortalities in hemodialysis (HD) [3–7] and non-dialyzed CKD patients [8–10]. Compared with serum PTH, which has a U-shaped or J-shaped association with mortality, serum ALP seems to have a linear and incremental association. Indeed, several guidelines, including the Japanese guideline, recommend the routine measurement of ALP in the management of CKD-MBD [11–13].

The incidence of hip fracture is high among dialysis patients and causes decreased quality of life (QOL) [14]. According to data from the United States Renal Data System (USRDS), the risk of hip fracture was 4.44 times higher for male and 4.40 times higher for female dialysis patients compared with people of the same sex in the general population [14]. In Japan, the incidences of hip fracture for male and female HD patients were 6.2 and 4.9 times higher, respectively [15]. Coco et al. [16] reported that the incidence of hip fractures was 17.4 times higher in HD patients than in the general population. Additionally, the average age at the time of hip fracture was younger than that of the general population, and 1-year mortality of HD patients with hip fractures was 2.7 times higher than HD patients without hip fracture and 2.4 times higher than the general population with hip fractures. Similarly, fracture HD patients had 3.7 times higher mortality compared with the overall HD population according to the Dialysis Outcomes and Practice Patterns Study (DOPPS) [17].

Several reports have demonstrated the association between ALP and the incidence of fracture in the HD population, but they included small numbers of fracture patients [4, 16, 18].

The aim of this study was to identify the effect of serum ALP levels not only on mortality but also on the incidence of hip fracture using a large cohort of Japan’s nationwide dialysis registry.

### MATERIALS AND METHODS

The Japanese Society for Dialysis Therapy has been conducting annual questionnaire surveys of dialysis facilities throughout Japan. This survey includes epidemiological background, treatment conditions and outcome of treatment of patients receiving dialysis. The number of patients undergoing dialysis at the end of 2009 was determined to be 290,661 [19]. Data were obtained with the permission of the Committee of the Renal Data Registry of the Japanese Society for Dialysis Therapy (JRDR). The standard analysis file (JRDR-10003) was used for this study. The study was conducted in accordance with the Declaration of Helsinki. The baseline data of 185,277 patients (age 66 ± 12 years, males 61.9%, and median HD duration of 5.8 years) receiving HD thrice weekly >90 days, who had available clinical data, were extracted (Table 1). Then, we evaluated clinical outcome, including mortality and the incidence of hip fracture using the data at the end of 2010.

Biochemical parameters including phosphorus, calcium, intact PTH, total ALP and albumin were measured by standard laboratory techniques in each center. Serum calcium values were corrected for serum albumin concentration using the formula corrected calcium (mg/dL) = total calcium (mg/dL) + 0.8 [4 – albumin (g/dL)]. Whole PTH, a parameter of 1–84PTH, was converted to intact PTH values by the following equation: intact PTH = 1 – 84PTH × 1.7. Cardiovascular mortality was defined as death caused by the following: heart failure, pulmonary edema, acute myocardial infarction, arrhythmia, endocarditis, valvular disease, subarachnoid hemorrhage, cerebral hemorrhage, cerebral infarction and sudden death. All other causes of death were defined as non-cardiovascular mortality.

#### Statistical analysis

Data are presented as means ± SD or medians and interquartile range (IQR). A P-value of <0.05 was considered significant. Characteristics of the population were categorized by quartiles of serum ALP, and they were compared through the one-way analysis of variance or the non-parametric Kruskal–Wallis test for continuous variables and the chi-square test for nominal variables. Multivariate logistic regression analysis was performed to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for the assessment of all-cause and cardiovascular mortalities and the incidence of hip fracture. In this analysis, the confounding factors were age, sex, HD duration, body mass index (BMI), underlying disease, comorbid disease including previous history of hip fracture, medication and laboratory data, listed in Table 1.

### RESULTS

A total of 185,277 HD patients were included, and their baseline characteristics by quartiles of serum ALP are shown in Table 1. Overall, the mean age was 66 ± 12 years, 61.9% was male, and the median HD duration was 5.8 years. The underlying disease was chronic glomerulonephritis in 70,954 (38.3%), diabetic nephropathy in 65,100 (35.1%), nephrosclerosis in
13 009 (7.0%), polycystic kidney disease in 6426 (3.5%) and others or unknown in 29 788 (16.1%). The numbers of patients who had a history of acute myocardial infarction, cerebral hemorrhage, cerebral infarction, quadruple amputation and hip fracture were 7.5, 4.8, 14.7, 2.9 and 2.9%, respectively. Regarding treatment for CKD-MBD, the percentages of patients administered with calcium carbonate, sevelamer hydrochloride, lanthanum carbonate, oral vitamin D, intravenous vitamin D and cinacalcet hydrochloride were 61.0, 28.7, 13.7, 38.2, 28.4 and 12.3%, respectively. Corrected calcium, phosphorus, PTH and ALP were 9.3 ± 0.9 mg/dL, 5.1 ± 1.5 mg/dL, 124 (63–208) pg/ml and 266 ± 144 U/L, respectively. Patients with higher ALP were older and more often female, and they had longer HD duration, lower BMI and more comorbidities, including acute myocardial infarction, cerebral hemorrhage, cerebral infarction, quadruple amputation and hip fracture. A higher ALP was also associated with lower albumin, lower blood urea nitrogen (BUN), lower creatinine (Cr), higher C-reactive protein (CRP), lower hemoglobin, lower corrected calcium, lower phosphorus and higher intact PTH levels. There were fewer users of calcium carbonate, sevelamer hydrochloride, lanthanum carbonate, and oral vitamin D and more users of intravenous vitamin D and cinacalcet hydrochloride in the higher ALP groups.

Of the 185 277 patients, patient status data were available for 179 916 patients at the end of 2010. Among them, 14 230 (7.9%) died of all causes, including 6396 (3.6%) cardiovascular deaths. Additionally, 151 748 patients had data on the presence or absence of hip fractures, and 1586 patients (1.0%) were newly diagnosed with hip fractures within the 1-year follow-up period. Figure 1 shows crude all-cause mortality (A), cardiovascular (CV) mortality (B) and the incidence of hip fracture (C) of deciles of serum ALP and quartiles of intact PTH.
ALP and hip fracture in HD patients

The major finding of this large cohort study including 185 277 HD patients was that a higher serum total ALP was significantly associated not only with increased mortality but also with the incidence of hip fracture. It appears that all of these associations were monotonic and incremental. It is the first large-scale report to demonstrate the association between fracture were higher in line with the increase of baseline serum ALP. Additionally, the patients with lower PTH levels had higher all-cause mortality and CV mortality. An association between the incidence of hip fracture and PTH levels was diminished. The results of multivariate logistic regression analysis are shown in Table 2. Patients in the highest quartile had higher all-cause and cardiovascular mortalities than those in the lowest quartile (OR 2.75, 95% CI 2.61–2.90; and OR 2.28, 95% CI 2.11–2.46, respectively). The associations were attenuated but still significant after adjustment for confounders (OR 1.46, 95% CI 1.33–1.60; and OR 1.25, 95% CI 1.10–1.42, respectively). In a stratified analysis, a higher serum ALP was more strongly linked to a higher mortality in the patients with lower PTH levels. Patients in the highest quartile had a higher incidence of hip fracture than those in the lowest quartile (OR 2.71, 95% CI 2.33–3.16). In the same manner, the associations were attenuated but still significant after adjustment for confounders (OR 1.71, 95% CI 1.33–2.18). In a stratified analysis, a higher serum ALP was more strongly linked to a higher incidence of hip fracture in the patients with lower PTH levels. Especially, serum ALP was not an independent predictor of the incidence of hip fracture among the patients in the highest quartile of PTH.

DISCUSSION

Table 2. Odds ratios and 95% CI of all-cause death, cardiovascular death and the incidence of hip fracture by baseline serum ALP level, according to quartiles of PTH

<table>
<thead>
<tr>
<th>PTH quartiles</th>
<th>&lt;63 pg/mL</th>
<th>63–123 pg/mL</th>
<th>124–208 pg/mL</th>
<th>&gt;208 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Continuous&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.018 (1.017–1.019)</td>
<td>1.0109 (1.009–1.013)</td>
<td>1.015 (1.011–1.018)</td>
<td>1.011 (1.007–1.015)</td>
</tr>
<tr>
<td>Quartile 1 (≤183)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Quartile 2 (184–235)</td>
<td>1.56 (1.47–1.65)</td>
<td>1.06 (0.96–1.16)</td>
<td>1.21 (1.03–1.42)</td>
<td>0.94 (0.78–1.13)</td>
</tr>
<tr>
<td>Quartile 3 (236–308)</td>
<td>1.94 (1.84–2.05)</td>
<td>1.24 (1.13–1.35)</td>
<td>1.35 (1.15–1.59)</td>
<td>1.23 (1.04–1.47)</td>
</tr>
<tr>
<td>Quartile 4 (≥309)</td>
<td>2.75 (2.61–2.90)</td>
<td>1.46 (1.33–1.60)</td>
<td>1.86 (1.58–2.18)</td>
<td>1.37 (1.15–1.64)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Continuous&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.011 (1.010–1.012)</td>
<td>1.005 (1.002–1.007)</td>
<td>1.006 (1.002–1.010)</td>
<td>1.006 (1.001–1.011)</td>
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<tr>
<td>Quartile 1 (≤183)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Quartile 2 (184–235)</td>
<td>1.46 (1.34–1.58)</td>
<td>1.02 (0.90–1.17)</td>
<td>1.15 (0.92–1.44)</td>
<td>0.87 (0.68–1.12)</td>
</tr>
<tr>
<td>Quartile 3 (236–308)</td>
<td>1.73 (1.60–1.88)</td>
<td>1.13 (0.99–1.28)</td>
<td>1.13 (0.90–1.42)</td>
<td>1.12 (0.89–1.43)</td>
</tr>
<tr>
<td>Quartile 4 (≥309)</td>
<td>2.28 (2.11–2.46)</td>
<td>1.25 (1.10–1.42)</td>
<td>1.59 (1.27–1.99)</td>
<td>1.23 (0.97–1.56)</td>
</tr>
<tr>
<td>Incidence of hip fracture</td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Continuous&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.012 (1.010–1.014)</td>
<td>1.011 (1.006–1.014)</td>
<td>1.015 (1.007–1.023)</td>
<td>1.015 (1.006–1.022)</td>
</tr>
<tr>
<td>Quartile 1 (≤183)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Quartile 2 (184–235)</td>
<td>1.42 (1.20–1.69)</td>
<td>1.19 (0.92–1.54)</td>
<td>1.21 (0.79–1.86)</td>
<td>1.20 (0.72–1.99)</td>
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<tr>
<td>Quartile 3 (236–308)</td>
<td>2.05 (1.75–2.40)</td>
<td>1.56 (1.25–1.99)</td>
<td>1.07 (0.68–1.69)</td>
<td>1.92 (1.20–3.08)</td>
</tr>
<tr>
<td>Quartile 4 (≥309)</td>
<td>2.71 (2.33–3.16)</td>
<td>1.71 (1.33–2.18)</td>
<td>1.82 (1.18–2.81)</td>
<td>1.71 (1.04–2.80)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ALP, alkaline phosphatase; PTH, parathyroid hormone.

<sup>a</sup>Adjusted for age, sex, HD duration, body mass index (BMI), underlying disease, comorbid disease, medication and laboratory data, listed in Table 1.

<sup>b</sup>Per 10 IU/L.
higher levels of serum ALP and the incidence of hip fracture. Additionally, we demonstrated for the first time that higher serum ALP was associated with higher risk of mortality in Japanese HD patients. It is meaningful to evaluate the impact of serum ALP on outcome in Japanese HD patients, because they show both a low mortality and low incidence of any fracture including hip fracture than US and European HD patients according to the DOPPS [17, 20].

Hip fracture is common among dialysis patients, and causes decreased QOL [14, 16] and indicates a poor prognosis [16, 17]. Serum total ALP is reported to be a predictor of hip fracture in HD patients. Blaney et al. [4] reported that a higher ALP was associated with a higher incidence of hospitalization for fracture in the analysis of the DOPPS study, but the fracture site was unknown, and the number of events (n = 460) was relatively small. Indeed, the clinical presentation of fracture in CKD varies by fracture site, especially between hip and vertebral fractures [21]. Coco et al. [16] analyzed 56 hip fracture patients on dialysis, and they found that age, albumin, PTH and ALP were independent predictors. Additionally, Kaji et al. [18] investigated 183 Japanese HD patients and found that serum ALP was significantly higher in HD patients with hip fracture than in those without hip fracture. In contrast, >180 000 HD patients were included in the present study, including >1000 patients with newly diagnosed hip fractures.

ALP is mainly a biochemical marker of bone turnover, and is usually used to monitor metabolic bone disease, particularly the management of CKD-MBD. A higher ALP might be associated with fracture through high bone turnover [2]. Indeed, Park et al. [22] found that serum ALP was negatively associated with bone mineral density assessed by dual-energy X-ray absorptiometry in HD patients. However, ALP is primarily secreted by the liver and bone, and a small amount is also secreted by the intestine, kidneys and leukocytes. Thus, monitoring of bone-specific ALP (BAP) is preferred in the assessment of bone mineral metabolism [23]. In a single-center cohort study, Limori et al. [24] investigated 485 HD patients with a median follow-up time of 39.9 months, and they found that serum BAP was associated with any type of incident fracture.

In the present study, a higher serum ALP was associated with an increased risk of both all-cause and cardiovascular mortalities. These findings correspond well to those of previous reports [3–6]. Shantouf et al. [25] reported that serum ALP was positively associated with coronary artery calcification score assessed by electron beam computed tomography in HD patients. There are several possible mechanisms to explain this association. Pyrophosphate, a small molecule constitutively produced by vascular cells, can block calcification and may be a natural inhibitor of hydroxyapatite formation, and ALP can promote vascular calcification by hydrolyzing pyrophosphate in the arterial wall [26, 27]. Inflammation also plays an important role, because atherosclerosis is well established to be an inflammatory process. Experimental studies have shown that proinflammatory cytokines stimulate production of an active metabolite of vitamin D in vascular smooth muscle cell (VSMC), and subsequently promote VSMC calcification through upregulating ALP expression [28, 29]. Damera et al. [30] reported that serum ALP is strongly associated with serum CRP, both in CKD and non-CKD populations.

ALP can be effectively lowered by both active vitamin D products [31] and calcimimetics [32]. In the present study, medications for CKD-MBD varied with the serum ALP level. Although the beneficial effect of these two drugs on patient survival were not determined by meta-analysis [33, 34], one can hypothesize that serum ALP is not only a prognostic factor but also a good target for the treatment of CKD-MBD in dialysis patients.

Here, we have to pay attention to the complex conditions of end-stage kidney disease. In particular, multiple risk factors including inflammation and malnutrition in a condition referred to as malnutrition-inflammation-cachexia syndrome were linked to poor outcomes in this population. Indeed, higher ALP levels were associated with lower BMI, albumin, BUN, Cr, phosphorus, and hemoglobin, and higher levels of CRP in the univariate analysis. Additionally, there is a possibility of the residual unsurveyed confounding factors that are also associated with the ALP. To prove the independent effect of serum ALP on outcomes, a prospective intervention trial to control serum ALP level is needed.

In a stratified analysis, a higher serum ALP was more strongly linked to a higher all-cause and CV mortality and the incidence of hip fracture especially in the patients with lower PTH levels. Serum ALP was not an independent predictor of the incidence of hip fracture among the patients in the highest quartile of PTH. PTH is also an important marker of CKD-MBD, and serum ALP are closely related with PTH in HD patients [35]. Many studies have indicated that PTH has a U-shaped or J-shaped association with mortality, and lower PTH levels were specially affected [36]. The effect of PTH on the incidence of hip fracture in dialyzed patients is inconclusive. Coco et al. identified a higher risk of hip fracture in patients with lower PTH levels (<195). On the other hand, Jadoul et al. [37] reported that PTH levels >900 were associated with an elevated risk of any new fracture versus PTH 150–300 in the analysis of the DOPPS study. Since the detailed interaction of ALP, PTH and other markers of CKD-MBD is really complicated, and combination of the markers rather than each parameter was associated with outcomes [38], it is necessary to take into account all these parameters comprehensively, when we estimate risks of HD patients.

Several limitations of the present study need to be mentioned. First, data about BAP were not collected, making the assessment of the effect of higher ALP on bone metabolism difficult. Drechsler et al. [5] reported that a higher BAP level was strongly associated with both all-cause and cardiovascular mortalities using the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) database, and they concluded that BAP assessment is more useful for treatment monitoring in dialysis patients than total ALP. However, routine measurement of BAP is difficult in clinical practice in Japan, because the cost of BAP measurement is approximately $20 per sample, compared with $1 for ALP measurement. Second, there were no data on liver function, which has an effect on serum total ALP. However, Regidor et al. [3] found that the association between increasing ALP and mortality remained consistent across the AST strata. Third, serum ALP and other
laboratory data were measured only at baseline; therefore we
could not examine the effect of changes from the baseline condition
during follow-up. Fourth, we could not perform time to
event analysis, which is the most appropriate way to analyze
cohort study data, because the database did not contain information
about date of occurrence of the event.

In summary, higher serum ALP levels were strongly associated
not only with mortality but also with the incidence of hip fracture in Japanese HD patients. Further studies are
needed to determine whether controlling of serum ALP levels
could improve the management of CKD-MBD.

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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Lau and Kalantar-Zadeh. Towards the
revival of alkaline phosphatase for the management of bone
disease, mortality and hip fractures. Nephrol Dial Transplant
2014;29:1450–1452.)

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A L P a n d h i p f r a c t u r e i n H D p a t i e n t s

1537
Urinary albumin excretion, blood pressure changes and hypertension incidence in the community: effect modification by kidney function

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ABSTRACT

Background. Both increased albuminuria and reduced kidney function may predict blood pressure (BP) progression in the community, while they exacerbate each other’s effects. We investigated associations and interactions between these two risk factors, BP changes and hypertension incidence in community-dwelling elderly men.

Methods. Observational study from the Uppsala Longitudinal Study of Adult Men, which included 1051 men (all aged 71 years) with assessments on urinary albumin excretion rate (UAER), 24-hour ambulatory BP monitoring (ABPM) and cystatin-C estimated glomerular filtration rate (eGFR). Of these, 574 men attended re-examination after 6 years, and ABPM measurements were again recorded to assess blood pressure changes and hypertension incidence.

Results. UAER was found to be associated with ABPM measurements both at baseline and longitudinally. In longitudinal analysis, there were significant interactions between UAER and kidney function in its association with the changes of systolic BP, mean arterial pressure and pulse pressure. After stratification for renal function state, UAER independently predicted BP changes only in those who had eGFR <60 mL/min/1.73 m². At re-examination, 71 new cases of hypertension were recorded. In multivariable logistic models, similar interactions were observed on hypertension incidence: UAER was an independent predictor of incident hypertension only in those with reduced renal function. These associations were evident also in the subpopulation of non-diabetics and in participants with normal range UAER (<20 µg/min).

Conclusions. In community-dwelling elderly men, UAER associates with BP progression and hypertension incidence, even within the normal range. Concurrent reduction of renal function modifies and exacerbates these associations.

Keywords: albuminuria, ambulatory blood pressure monitoring, chronic kidney disease, hypertension, urinary albumin excretion