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Permalink

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Journal

Hemodialysis International, 18(4)

ISSN

1492-7535

Authors

Lau, Wei Ling

Kalantar-Zadeh, Kamyar

Kovesdy, Csaba P

et al.

Publication Date

2014-10-01

DOI

10.1111/hdi.12190

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Peer reviewed

Alkaline phosphatase: Better than PTH as a marker of cardiovascular and bone disease?

Chronic kidney disease (CKD) is complicated by alterations in mineral homeostasis that increase the risk for ectopic calcification (vascular calcification being of particular concern) and bone disease, a syndrome that has been labeled CKD mineral and bone disorder (CKD-MBD). In terms of bone disease and fracture risk, bone biopsy is the gold standard diagnostic tool but is rarely performed in clinical practice due to its invasive nature. A reliable serum biomarker of bone disease that could guide medical management would be highly valuable, given the increased risk of hip fractures in patients with CKD and end-stage renal disease (ESRD),^{1–5} whereby hip fracture is associated with increased mortality.^{3,6,7} Currently, parathyroid hormone (PTH) is the most widely referenced CKD-MBD biomarker in clinical practice, and the 2009 Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest a target PTH range of two to nine times the upper limit of normal (approximately 130–585 ng/L) in maintenance dialysis patients.⁸ Target PTH range is not specified for pre-dialysis patients with CKD. As will be discussed in more detail below, PTH can vary significantly when repeat measurements are taken in a stable dialysis patient, and there is growing evidence that alkaline phosphatase (ALP) may be a more accurate biomarker of bone turnover.

ALP enzymes are membrane bound and catalyze hydrolysis of monophosphate esters at alkaline pH. In humans, the four ALP isozymes include tissue non-specific ALP, intestinal ALP, placental ALP, and germ cell ALP.⁹ Of particular interest in CKD is tissue non-specific ALP, which exists as numerous isoforms that differ primarily in extent and type of glycosylation.¹⁰ The bone and liver isoforms of tissue non-specific ALP make up approximately 95% of total serum ALP activity in healthy adults, in equal

proportions. Bone ALP is an ectoenzyme anchored to the membrane of osteoblasts and thus reflects overall bone remodeling.⁹ Total serum ALP was historically used to guide management of patients with CKD, but its use was limited by its non-specificity for bone disease and undefined target range. Alkaline phosphatase is not mentioned in the 2002 Kidney Disease Outcomes Quality Initiative guidelines, but makes an appearance in the 2009 KDIGO guidelines—this attests to growing recognition of the prognostic value of ALP. However, the KDIGO guidelines are vague, suggesting measurement of ALP every 12 months, or more frequently if PTH is not at target, and no target range is specified.⁸

Intuitively, it makes sense to measure an enzyme that is directly involved in bone and vascular wall activity in our assessment of CKD-MBD, as compared with PTH that is fundamentally more reflective of parathyroid gland activity than bone remodeling.¹¹ As a potential biomarker of CKD-MBD, ALP may be superior compared with PTH as it shows less within-individual biological variation.^{12,13} PTH has a very short half-life of 2–4 minutes, whereas bone ALP has a half-life of 1.5–2.3 days and the liver isoform has a half-life of 5–9 days.¹⁴ In a hemodialysis patient, calculations extrapolated from PTH variability suggest that 26 specimens need to be measured to estimate a PTH homeostatic set point within $\pm 10\%$ with 95% probability, whereas four samples would be needed to estimate the true value of blood ALP.^{12,15} Aside from this biologic variability, analytical variation is also a problem since a variety of second- and third-generation PTH assays are commercially available and there is lack of standardization between clinical laboratories. Souberbielle et al. compared PTH levels measured with 15 commercial immunoassays in 47 serum pools from dialysis patients, and reported a median bias of –44.9 to 123% using the Allegro second-generation assay as a reference.¹⁶ In contrast, ALP is measured along with standard serum chemistries in automated bioanalyzers.

Correspondence to: W. L. Lau, MD, 101 The City Drive South, City Tower, Orange, CA 92868-3217 U.S.A. E-mail: willau@uci.edu

The clinician should keep in mind that interpretation of total ALP is not straightforward in maintenance dialysis patients. One cannot always assume that an increase in serum total ALP reflects increased bone ALP activity if hepatobiliary markers such as gamma-glutamyl transferase (GGT) are normal. Many hemodialysis patients with increased bone ALP levels will have normal total ALP activity.¹⁷ Intestinal ALP levels can be elevated in dialysis patients and thus confound interpretation of total ALP.^{18,19} Liver ALP may be particularly significant in the setting of hypervolemia. Ortega and colleagues conducted an elegant study demonstrating elevated liver ALP in patients with CKD with fluid overload, whereby subclinical liver congestion was proposed as the cause of elevated total ALP.²⁰ The authors showed that intensified diuretic therapy decreased body weight and GGT, and concurrently lowered serum ALP.

Although some experts propose specific measurement of bone ALP to evaluate bone turnover,⁹ clinical utility of detecting various isoforms of tissue non-specific ALP remains unclear. Fahrleitner-Pammer et al.²¹ found that bone-specific ALP correlated with increased cardiovascular events in a prospective cohort study of 135 patients with CKD, and Kobayashi et al.²² found a similar trend in 196 male hemodialysis patients followed for 5 years. However, Filipowicz and colleagues reported that skeletal ALP was not associated with inflammation (higher C-reactive protein levels) or mortality in 10,707 non-CKD and CKD participants from the 1999–2004 National Health and Nutrition Examination Survey cohort.²³ A lack of association between bone-specific ALP and long-term hip fracture risk was also shown in older adults without CKD.²⁴

From a pathophysiologic standpoint, quantifying relative amounts of ALP isoforms may be irrelevant since ALP ultimately, regardless of source, promotes abnormal calcification of blood vessels. Circulating ALP is proposed to degrade pyrophosphate, an endogenous anti-calcification factor in the vessel wall.^{25,26} In vitro, Lomashvili et al. reported that addition of ALP resulted in elastic wall calcification of cultured rat aorta,²⁵ whereas inhibition of ALP's pyrophosphatase activity has been shown to reduce rat aortic calcification.²⁷ Vascular smooth muscle cells (VSMCs) undergo a phenotype transformation when subjected to a pro-mineralization milieu, and expression of bone ALP has been detected in calcifying human VSMCs.^{28,29} This vascular wall bone-like activity may propagate vascular calcification and subsequent cardiovascular events. In terms of fracture risk, mouse knockout models attest to the central role of ALP in bone mineralization,^{30,31} however, overexpression studies have not been carried out.

In contrast, many studies have found *total* ALP to be a strong predictor of adverse outcomes in the CKD and dialysis populations. Higher ALP levels in CKD correlate with increased mortality and progression to ESRD, as well as progressive peripheral arterial calcification.^{32–35} There is a similar association between higher total ALP levels and increased mortality in maintenance hemodialysis and peritoneal dialysis patients, and ALP correlates with coronary artery calcification (CAC) score in hemodialysis patients.^{36–44} Further, in terms of bone fracture risk, higher ALP predicts hip fracture risk and decreased bone mineral density in hemodialysis patients.^{39,41,45,46}

In the recent issue of *BMJ Open*, Beige and colleagues retrospectively studied the association of skeletal ALP and total ALP on mortality outcomes in 407 maintenance dialysis patients in Germany (~4% were on peritoneal dialysis, the remainder were hemodialysis patients).⁴⁷ Patients were dichotomized by total ALP level averages into two equal-sized strata divided at 77.5 U/L. Odds ratio (OR) of all-cause death in the higher ALP stratum was significantly higher during the 5-year follow-up period, compared with patients in the lower ALP stratum (OR 2.70, 95% confidence interval 1.76–4.15). Bone-specific ALP had a weaker association with mortality that carried the same trend (the higher the lowest ever measured bone ALP for an individual patient, the higher the risk of mortality); however, this association disappeared when total ALP was not included in Cox models. Although the study is not particularly novel, the robust OR for death is startling for a relative small sample size, and the loss of mortality predictability of bone-specific ALP when Cox stepwise regression was performed without total ALP further supports the notion that measurement of skeletal ALP may not be clinically useful.

Total ALP appears to be a more consistent predictor of adverse outcomes than PTH in several studies. Although PTH generally has a U-shaped association with mortality, in a cohort of almost 74,000 hemodialysis patients total ALP had a linear and incremental association with both all-cause and cardiovascular mortality (Figure 1), an association that held true across different PTH strata including PTH <150 pg/mL.⁴⁸ This linear association with mortality was also shown in men with pre-dialysis CKD.²⁴ Another study found that elevated ALP, but not PTH, was associated with increased CAC in hemodialysis patients, with total ALP >120 U/L being a robust predictor of CAC.⁴⁴ In kidney transplant recipients, pre-transplant elevated ALP levels correlate with increased post-transplant mortality; PTH levels did not show any association.⁴⁹ We are in agreement with others who have voiced concerns regarding the use of PTH in our clinical guidelines for ESRD care.^{50,51}

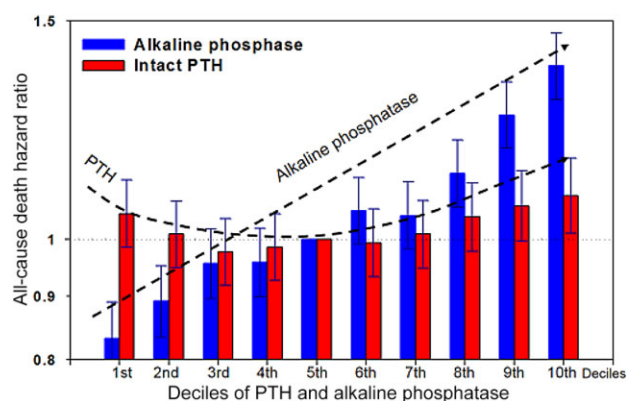


Figure 1 Comparing mortality predictability of deciles of serum alkaline phosphatase (ALP) and deciles of intact parathyroid hormone (PTH) in 73,960 maintenance hemodialysis patients who were followed for up to 3 years (2001–2004). Analyses are based on fixed covariate (non-time dependent) and fully adjusted models. The fifth decile serves as the reference group. The cut-off levels for ALP deciles are 61, 71, 79, 87, 96, 107, 121, 142, and 186 U/L and for intact PTH are 64, 106, 146, 184, 224, 274, 344, 459, and 697 pg/mL. Each decile includes approximately 7,400 maintenance hemodialysis patients. Hazard ratios in y-axis are in logarithmic scale. Adapted from Regidor et al.⁴⁰

Effective therapies exist for lowering of ALP: both activated vitamin D products and calcimimetics have been shown to lower circulating ALP.^{52,53} Thus, the traditional marker ALP is a promising tool that has the potential to guide CKD-MBD management. However, as with many other areas in CKD we lack prospective data, and it is currently unknown whether lowering of ALP would alter mortality and fracture outcomes. Prospective randomized trials are needed to determine optimal ALP targets in patients with CKD and ESRD.

Wei Ling LAU, MD,
Kamyar KALANTAR-ZADEH, MD, MPH, PhD
Orange, CA
Csaba P. KOVESDY, MD
Memphis, TN
Rajnish MEHROTRA, MD, MS
Seattle, WA

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