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Towards the revival of alkaline phosphatase for the management of bone disease, mortality and hip fractures

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IN FOCUS

The story of alkaline phosphatase in the management of mineral and bone disorder (MBD) in patients with chronic kidney disease (CKD) is an interesting and educational part of the history of nephrology. Circulating alkaline phosphatase, a marker of bone turnover, was among the first bone markers used for the detection and management of 'renal osteodystrophy', a term previously used by clinicians and researchers since the 1970s. However, by the mid-1990s and early 2000s alkaline phosphatase fell out of favor, when commercial parathyroid hormone (PTH) assays become available. At the same time, the first Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines on CKD–MBD chose not to mention alkaline phosphatase, as target ranges were uncertain [1]. A rise in serum alkaline phosphatase, known as hyperphosphatasemia or hyperphosphatasia, is an expected finding in progressive CKD with worsening kidney function [2]. Elevated serum alkaline phosphatase concentrations in CKD patients with otherwise intact liver and biliary systems usually result from excess of the bone isoforms of the enzyme [3–5]. Specific detection of the bone isoform may not have clinical utility, since it was found not to correlate with inflammation or mortality risk [6]. The recent data suggest that a rise in alkaline phosphatase in dialysis patients is associated with worsening bone mineral density [7], and worse responsiveness to erythropoiesis stimulating agents [8].

The existence of an incremental and strictly linear associations between higher serum alkaline phosphatase (>120 U/L) and worse mortality was reported first in hemodialysis patients [9, 10], and more recently in peritoneal dialysis patients [11] as well as in non-dialysis dependent CKD patients [12–14]. At least in dialysis patients, these findings are in sharp contradistinction to the mortality predictability of serum PTH, which has a U-shaped relationship in that both high and low PTH are associated with higher death risk [10]. Even more importantly, the alkaline phosphatase-death association persists even across different PTH strata including when PTH is <150 pg/mL [9, 10]. Interestingly, a low alkaline phosphatase level is associated with greater survival, a finding that appears to question the harmfulness of adynamic bone disease. These studies suggest that alkaline phosphatase is more than a mere marker of high-turnover bone disease and may serve a reliable mortality predictor. Hence, modulating alkaline phosphatase via interventions such as improving CKD care, better dialysis treatment, or therapy with vitamin D agents or calcimimetics, may improve not only bone health but also survival of CKD patients.

Higher circulating alkaline phosphatase may increase hydrolysis of pyrophosphate [15, 16], which is a potent inhibitor of vascular calcification [17–19]. The modulatory effect of alkaline phosphatase on pyrophosphate could be the link as to why lower levels of the former are associated with an incremental drop in mortality [20]. Consistent with this notion, a recent epidemiologic study found that higher levels of alkaline phosphatase (and not PTH, calcium or phosphorus) were associated with coronary artery calcification in hemodialysis patients [21]. Higher alkaline phosphatase levels are also associated with lower 25(OH) vitamin D level [22–24], which is *per se* associated with increased mortality [25].

In this issue of *Nephrology Dialysis Transplantation*, Maruyama *et al.* [26] examined the baseline data in 185 277 prevalent hemodialysis patients in Japan and related them to 1-year mortality and incident hip fracture events through calendar year 2010. They found that patients in the highest quartile of serum alkaline phosphatase had 46% and 25% higher all-cause and cardiovascular death risk, respectively, as well as a 71% higher incidence of hip fracture events, than those within the lowest quartile [26]. Whereas the mortality predictability of alkaline phosphatase is a well-known finding, this is the first report of such an association in a large cohort of Japanese dialysis patients. It is important to note that Japanese dialysis patients have by far the best survival among all known dialysis patients in the world, usually <10% per year, when compared with European and US dialysis patients who have an annual mortality of 15–20% or higher [26]. Japan is also the nation with the longest life expectancy of 92 years. Maruyama *et al.* reported an annual mortality of 7.9% in their

national Japanese cohort of over 150 000 hemodialysis patients, once again confirming the consistency of survival superiority in Japanese dialysis patients.

An even more novel and clinically relevant finding by Maruyama *et al.* [26] is the association of high serum alkaline phosphatase with bone fracture. During 1-year follow-up 1586 patients, or ∼1% of the national cohort, experienced a new hip fracture. The odds ratio of hip fracture was 1.71 with a 95% confidence interval of 1.33–2.18. This adds to the growing evidence that points to alkaline phosphatase as a circulating marker for hip fracture risk [27, 28]. That this finding comes from Japanese patients is even more important, since Japan is one of the very few countries in the world that does not endorse or implement Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD-MBD, which suggests a target PTH range of 150–600 pg/mL (2–9 times above the upper threshold); in Japan the target PTH range is 60–360 pg/mL [29]. Indeed, during the pre-KDIGO era, when the US KDOQI recommendations of 2002 suggested a PTH range of 150–300 pg/mL, Japan had an even lower target range of PTH of 60–180 pg/mL [29], a range that might be considered too low and a cause of adynamic bone disease by some West European and North American opinion leaders [29]. These low levels of PTH are usually achieved by administering high doses of active vitamin D, in particular maxacalcitol in Japan. Maxacalcitol is a vitamin D mimetic of D3 type with similarities to its D2 counterpart paricalcitol, which *per se* may be associated with survival advantages [30], when compared with other vitamin D analogs, including calcitriol (D3), 1-alpha (OH)-calciferol (D3) and 1-alpha-(OH)-ergocalciferol (D2), also known as doxercalciferol [31]. Whereas there are no clear data about the differential effect of these vitamin D analogs on PTH level or alkaline phosphatase, there is little doubt that all these agents [32], as well as calcimimetics [33], effectively lower alkaline phosphatase by ameliorating the activity of bone turnover.

Serum alkaline phosphatase is measured usually monthly to quarterly in all dialysis patients in most countries in the world and provides an excellent bone marker to monitor bone health in CKD, when compared with PTH which is a hormone from parathyroid glands, not bone, with only secondary impact on the bone. Hence, it is logical to use a direct bone marker rather than a non-bone-based hormone when the goal is to evaluate bone turnover. Given recent data that indicate a biologically plausible link between pyrophosphate degradation by tissue-non-specific alkaline phosphatase as a causative pathway in vascular calcification [15, 20], and given the lower bone density reported in dialysis patients with higher alkaline phosphatase levels [7], the data by Maruyama *et al.* [26] makes sense and is strong supportive evidence that alkaline phosphatase should be monitored more judiciously. High alkaline phosphatase levels of >120 IU/L has been suggested as a mortality cutoff by Regidor and colleagues [9]. The consistency of epidemiologic and experimental data on alkaline phosphatase and the effective lowering of alkaline phosphatase by vitamin D analogs and calcimimetics make this traditional marker a promising tool for the management of CKD–MBD, irrespective of the disappointing fact that current KDOQI and KDIGO guidelines still have a major gap and disconnect from the data on alkaline phosphatase. There is prevailing concern with adynamic bone disease despite lack of epidemiological data to back this obsession. High-turnover bone disease, rather than adynamic bone disease, has clearly been associated with increased harm and may be a major culprit in the high death risk and hip fracture rate in dialysis patients. Measuring PTH and other circulating mineral markers without paying adequate attention to a marker that is truly of bone source, i.e. alkaline phosphatase, makes little sense; however, this unbalanced approach dominates current clinical practice. The recent data about the importance of alkaline phosphatase in dialysis patient outcomes are overwhelming [34–37]. We look forward to the needed heightened attention to serum alkaline phosphatase levels in the management of MBD in dialysis patients.

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CONFLICTS OF INTEREST STATEMENT

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(See related article by Maruyama *et al.* A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among patients receiving hemodialysis in Japan. *Nephrol Dial Transplant* 2014; 29: 1532–1538.)

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