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Narrative Review

Bone Alkaline Phosphatase in CKD–Mineral Bone Disorder

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Overall and cardiovascular mortality in patients with chronic kidney disease (CKD) is greatly increased, without obvious current effective treatments. Mineral and bone disorder (MBD) is a common manifestation of CKD and contributes to the high risk of fracture and cardiovascular mortality in these patients. Traditionally, clinical management of CKD-MBD focused on attenuation of secondary hyperparathyroidism due to impaired renal activation of vitamin D and phosphate retention, although recently, adynamic forms of renal bone disease have become more prevalent. Definitive diagnosis was based on histologic (histomorphometric) analysis of bone biopsy material supported by radiologic changes and changes in levels of surrogate laboratory markers. Of these various markers, parathyroid hormone (PTH) has been considered to be the most sensitive and currently is the most frequently used; however, the many pitfalls of measuring PTH in patients with CKD increasingly are appreciated. We propose an alternative or complementary approach using bone alkaline phosphatase (ALP), which is directly related to bone turnover, reflects bone histomorphometry, and predicts outcomes in hemodialysis patients. Here, we consider the overall merits of bone ALP as a marker of bone turnover in adults with CKD-MBD, examine published bone histomorphometric data comparing bone ALP to PTH, and discuss possible pathogenic mechanisms by which bone ALP may be linked to outcomes in patients with CKD.

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Chronic kidney disease (CKD) is associated with adverse outcomes, including progressive kidney failure, cardiovascular disease, and premature death. A 40-fold higher cardiovascular disease death rate has been reported in hemodialysis patients compared with the general population,[1] and of CKD deaths, cardiovascular disease accounts for nearly 50%.[2] CKD is complicated by characteristic biochemical derangements, including alterations in mineral homeostasis and the development of CKD–mineral and bone disorder (CKD-MBD).[3,4] Classically, this consisted of secondary hyperparathyroidism and concomitant high-turnover bone disease in response to decreased renal activation of vitamin D and phosphate retention. More recently, low-turnover adynamic bone disease has become more prevalent. Although definitive diagnosis has always required bone biopsy, with the advent of readily available and seemingly reliable parathyroid hormone (PTH) assays through the later 1980s and beyond, nephrologists increasingly came to rely mainly on PTH measurement as their primary skeletal health assessment tool. The limitations of PTH in this regard increasingly are realized.[5] Here, we consider the biology, pathophysiology, measurement, and relative merits of an alternative marker of CKD-MBD; that is, bone alkaline phosphatase (ALP). Bone ALP is related directly to bone turnover, reflects bone histomorphometry, and predicts outcomes in hemodialysis patients. Although assays have been available for 20 years, bone ALP has been largely overlooked in clinical practice as a marker of CKD-MBD. We present the rationale for the use of bone ALP as a marker of CKD-MBD.

CKD-MBD AND PTH

As kidney disease progresses and glomerular filtration rate decreases, hyperphosphatemia occurs, along with a reduction in renal 1α-hydroxylation of 25-hydroxyvitamin D and low circulating levels of calcidiol, which in turn decreases intestinal calcium absorption. To maintain calcium and phosphate homeostasis, patients with CKD develop variable degrees of secondary hyperparathyroidism, with concomitant abnormalities in bone turnover and metabolic bone disease. This is seen clinically as bone pain and is reflected in a dramatically increased incidence of and fatal sequelae from hip fracture in dialysis patients,

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with fracture occurring at a younger age than in the general population.[6-8]

According to the KDIGO (Kidney Disease: Improving Global Outcomes) guideline, CKD-MBD describes the "broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD."[9(pS3)] This includes high-turnover bone disease, but also other forms of bone disease in addition to vascular calcification (discussed later). The categories of bone disease in CKD include high-turnover bone disease states, including osteitis fibrosa; low-turnover bone disease states, including adynamic bone disease; osteomalacia; and mixed uremic osteodystrophy. Although traditionally high-turnover bone disease predominated in patients with kidney failure, recently there appears to have been a shift toward predominance of low-turnover bone disease, especially in white populations.[10] Osteomalacia and mineralization defects also appear to be rarer than hitherto thought.

The gold standard for diagnosis of the bone component of CKD-MBD is biopsy-based histomorphometric analysis. Histologic findings are classified by determining bone turnover (rate of bone remodelling in the coupled process of formation and resorption), mineralization (assessing the osteoid), and volume (the balance between bone formation and resorption).[9,11] Bone biopsy is an invasive procedure now rarely performed in clinical practice in some countries. Instead, clinical management is based largely on the use of surrogate laboratory markers. Guidelines for CKD-MBD management currently recommend measurement of ALP, PTH, and 25-hydroxyvitamin D, with PTH concentration commonly considered the most sensitive marker of underlying disordered metabolism.[9] Recommendations for patients receiving dialysis are to target PTH concentrations to 2-9 times the upper limit of the reference range (for the assay in use) and to make therapeutic decisions based on trends rather than single values.[9] There currently are no worthwhile PTH target range recommendations for patients with CKD not receiving dialysis.

The use of PTH concentration has serious limitations in this setting.[5] The relationship between bone histology and PTH concentration is inconsistent, with PTH being poor at discriminating between low- versus high-turnover bone disease, especially in the range of 100-1,000 ng/L, where most patients' PTH concentrations lie.[12,13] Furthermore, the relationship between PTH and underlying bone changes appears to be influenced strongly by race[10,14] and affected by skeletal resistance to the action of PTH in the uremic state.[15] Other pitfalls of measuring PTH include analyte instability,[16] accumulation of inactive or nonclassically active carboxy-terminal forms of PTH (eg, PTH_{7-84}, a form lacking the first 6 amino acids),[17,18] assay variability,[19-23] and high biological variation.[24] Recently, the formation of oxidized biologically inactivated PTH has been demonstrated in patients with kidney failure.[25] The extent of oxidation varies between individuals, but may be significant: such inactivated PTH remains detectable by immunoassay. As a consequence of the shortcomings of PTH as a marker, there is an urgent clinical need to identify better markers of CKD-MBD.[5]

BIOLOGY OF BONE ALP

ALP Isozymes

ALP (Enzyme Commission classification number EC 3.1.3.1) encompasses a heterogeneous group of membrane-bound enzymes that catalyze the hydrolysis of monophosphate esters at alkaline pH. In humans, there are 4 gene loci encoding ALP isozymes; in other words, tissue-nonspecific ALP encoded by the *ALPL* gene, intestinal ALP (*ALPI*), placental ALP (*ALPP*), and germ cell ALP (*ALPPL2*). The tissue-specific ALPs (ie, intestinal, placental, and germ cell ALP) are clustered on chromosome 2, bands q34.2-q37, and are 87%-98% homologous to each other, but only ~50% identical to tissue-nonspecific ALP, which is located on chromosome 1, bands p36.12.[26-28] While the tissue-nonspecific ALP gene is not highly polymorphic, its gene product exists as numerous isoforms in biological fluids, differing primarily in the extent and type of glycosylation,[29-31] most notably the bone ALP and liver ALP isoforms. Approximately 95% of total ALP activity in serum of healthy adults constitutes bone and liver ALP, found in approximately equal proportions.[32] Hence, if the activity of other hepatobiliary enzymes such as γ-glutamyl transferase is normal, then an increase in total ALP usually reflects increased bone ALP activity. However, this assumption wrongly identifies the source of elevated ALP activity in some hemodialysis patients, and many patients with increased bone ALP levels will have normal total ALP activity.[33] Increases in intestinal ALP levels also have been widely reported in dialysis patients.[34,35] Changes, increases or decreases, in bone ALP levels may be masked by changes in activities of other ALP isozymes and isoforms when total ALP is measured. Consequently, specific measurement of bone ALP is required to provide secure information relating to bone ALP status.

Function of Bone ALP

Bone ALP is a homodimeric glycoprotein; as an ectoenzyme, it is anchored to the membrane of osteoblasts through glycosylphosphatidylinositol (GPI).[36,37] Consequently its activity is a general indicator of the

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