ABSTRACT

Hyperphosphatemia is an independent risk factor for mortality in patients with end-stage renal disease, in addition to those with less severe forms of chronic kidney disease. The specific reasons for this association remain speculative. However, serum phosphate levels and cardiovascular disease have been correlated across a range of renal dysfunction. Recent studies indicate that in addition to well-established effects on osseous tissue, elevated serum phosphorus levels increase risk of soft-tissue calcification and arterial stiffness. These changes are, in turn, associated with increased cardiovascular risk. Interestingly, exposure to high extracellular phosphate concentrations has been shown to induce osteogenic gene expression in vascular smooth muscle cells. The relationships among specific forms of renal osteodystrophy, calcium load, and phenotypic expression in vascular smooth muscle cells raise some intriguing questions about the contributions of phosphate metabolism and cardiovascular risk. This article will address these questions and their implications for therapeutic intervention.

and are therefore pertinent for the overall care of patients with CKD.4 Despite the description of these abnormalities in connection with renal osteodystrophy more than 30 years ago, the relationship with soft-tissue calcification was not widely appreciated.5

Some metabolic disturbances of CKD are associated with bone disease and with cardiovascular disease. For example, exposures to abnormally elevated concentrations of phosphorus in the serum, particularly in patients with an estimated GFR below 60 mL/min/1.73 m2, may provide clues to this link.6,7 In patients with CKD who have not yet progressed to ESRD, serum phosphate levels above 3.5 mg/dL have been significantly associated with increased risk of death.8 Recently, a significant and graded association between baseline serum phosphate concentration and the risk of death and cardiovascular events was demonstrated in select patients with less severe decrements in GFR.9 These strong associations have led to speculation that increased concentrations of serum phosphorous levels promote loss of vessel compliance, increase cardiac load, and lead to overt arterial calcification.

This article will explore the relationship of renal osteodystrophy, serum phosphate levels, and the expanding body of evidence that vascular and coronary calcifications may be one of the CKD-specific factors that contribute to cardiovascular risk. The implications for treatment of hyperphosphatemia will also be discussed.

**MINERAL METABOLISM AND RENAL OSTEODYSTROPHY**

Traditionally, the abnormal mineral metabolism that occurs in patients with CKD was considered to manifest primarily in the osseous tissues. Because PTH and calcitriol (1,25-dihydroxyvitamin D3) play a pivotal role in the regulation of bone turnover, the altered mineral and hormone metabolism that accompanies renal failure leads to significant changes in bone known as renal osteodystrophy.9 As described earlier in this article, renal osteodystrophy can be categorized into 4 subtypes: mixed uremic osteodystrophy, hyperparathyroid bone disease, adynamic bone disease, and osteomalacia (Figure 1).3,9

**HIGH-VERSUS LOW-TURNOVER BONE DISEASE**

Bone lesions of excess PTH (high-turnover bone disease) are associated with increased osteoclastic and osteoblastic activity.3 This is characterized on bone biopsy by an expanded population of osteoblasts depositing unmineralized bone and by increased surface area of bone resorption by osteoclasts. The enhanced bone resorption induced by high levels of PTH releases calcium and phosphorus from the skeleton into the extracellular fluid. However, because renal phosphate excretion is compromised, serum phosphate levels increase.3

Bone lesions of defective mineralization in CKD, presenting in severe cases as osteomalacia (low bone turnover), are the characteristic defects associated with aluminum overload. Vitamin D deficiencies (relative or absolute) also may contribute to defective mineralization. Features of osteomalacia include wide osteoid seams and increased osteoid volume, particularly when the volume is compared to the amount of surrounding mineralized tissue.4

Adynamic bone disease (low-turnover bone disease) is characterized by defective bone matrix formation and mineralization, thin osteoid seams, and decreased numbers of osteoclasts and osteoblasts.3 Even to the untrained eye, these changes present sharp contradistinction to high-turnover osteodystrophy. In addition, adynamic bone disease contrasts with osteomalacia because of absence of osteoid accumulation. Aside from aluminum accumulation, this condition is associated with excessive
suppression of the parathyroid gland with high calcium intake and/or administration of calcitriol. Bone lesions may develop with relatively normal PTH levels because it is generally accepted that the blood levels of PTH needed to maintain normal rates of bone formation are above the normal level.3

**RENAL OSTEODYSTROPHY AND SOFT-TISSUE CALCIFICATION**

Traditionally, renal osteodystrophy and soft-tissue calcification have been considered to be distinct and independent consequences of abnormal mineral metabolism in CKD. However, if bone is recognized as a tremendous reservoir of calcium and phosphorus, it seems not unlikely that the turnover of bone would predispose a patient with CKD to calcification of critical soft tissues. As depicted in Figures 2 and 3, the ongoing processes in the body compartments may be less disparate than previously considered.

In patients with low-turnover bone disease, for example, hypercalcemia may result from low-to-normal plasma calcium efflux and low bone calcium accretion (Figure 2). These patients are unable to incorporate extra calcium into the bone matrix, increasing the risk of hypercalcemia. This condition could shift the equilibrium toward soft tissues, a set of circumstances that might promote calcification of vital soft tissues (Figure 2). In one study in a small cohort of hemodialysis patients, features of low-turnover bone disease correlated with calcification of arterial beds. 10

In contrast, patients with CKD with increased bone turnover secondary to elevated action of PTH release calcium and phosphate from the skeleton into the extracellular fluid (Figure 3). However, because renal excretion is reduced, serum levels of these minerals increase. In addition, PTH enhances movement of calcium into cells, which may further contribute to soft-tissue calcification. Therefore, one could speculate that either extreme of underlying renal bone disease, either low- or high-turnover states, might predispose to calcification of nonosseous tissues. One manifestation of this could be calcification of cardiac tissues.

**CARDIOVASCULAR CALCIFICATION**

Dramatic and extensive calcification has been demonstrated in the coronary arteries of patients with ESRD and, for nearly 10 years, it has been recognized that this process occurs in ESRD regardless of patient age. In patients with ESRD, the prevalence of elevated coronary artery calcification scores (typically assessed with electron-beam computed tomography [CT] scanning) ranges from 80% to 95%, whereas the prevalence of coronary calcification in pre-ESRD patients ranges from 55% to 100%. However, it is difficult to compare published series because the methods and thresholds for determining calcification are not standardized.
It appears that diabetes is an important clinical cofactor, particularly in patients with stages 3 to 4 CKD. Furthermore, detection of vessel calcification prior to ESRD is not consistently correlated with serum markers of abnormal mineral metabolism. These observations suggest that the pathogenesis of vessel calcification is complex, particularly in the early stages of CKD. In addition, it is apparent that vascular calcification, at least as detected by CT scanning, is heterogeneous. Patients with CKD are more likely to manifest calcifications in the medial wall of the artery; these lesions are characterized by diffuse mineral deposits within the arterial tunica media. These deposits are morphologically distinct from calcification of atherosclerotic plaques, usually distributed less continuously and in the intima of the vessel (Figure 4). Recently, Block et al reported that the extent of coronary artery calcification is an important predictor of outcome once a patient enters stage 5 CKD. Therefore, a better understanding of the process that leads to vessel calcification may lead to improved outcomes.

Although intimal and medial calcifications both can contribute to cardiovascular risk, they do so through somewhat different mechanisms. Intimal calcification occurs when minerals are deposited in atherosclerotic plaques that are typically located in the intima of the arterial wall. The calcification that results from mineral deposition within plaques is not specific to CKD, although it may be more severe in patients with ESRD. Calcified intimal lesions are patchy, irregular lesions restricted to the area around the atheroma and typically do not affect the surrounding intima.

In contrast, medial calcification is characterized by diffuse calcified deposits within the arterial tunica media. Although it may increase with age in many individuals, the incidence of medial calcification is greatly increased in patients with metabolic disorders, such as the metabolic syndrome, diabetes, and CKD. The arterial stiffness that may result can lead to elevated pulse-wave velocity and loss of vascular compliance. Some investigators have been able to demonstrate an association among abnormal serum calcium and phosphorus and these “early” functional abnormalities of arterial beds in CKD. It is possible that medial calcification is accompanied by elevated aortic and left ventricular systolic pressures and increased cardiac workload. These changes increase oxygen consumption and lead to left ventricular hypertrophy and diastolic dysfunction.

Regardless, intimal and medial deposition of calcium within arterial walls occurs commonly in patients with ESRD, and either process is associated with poor prognosis in this high-risk population. In a large group of hemodialysis patients, soft-tissue radiograms were analyzed for the presence and type (medial versus intimal) of arterial calcifications. As anticipated, intimal calcification was often observed in older patients with a clinical history of atherosclerosis and with traditional risk factors. In contrast, medial calcification was observed in younger patients that lacked traditional risk factors, and it was more closely associated with dialysis vintage and with prescription of oral calcium-containing phosphate binders. This study also demonstrated a unique mortality risk associated with medial and intimal calcification.
lar risk. However, the processes that promote arterial calcification remain obscure. One scheme is based on experiments in arterial smooth muscle cells, and it proposes that extracellular phosphorus (and hyperphosphatemia) plays a central role in the process. In these experiments, isolated smooth muscle cells in culture can be induced to shift phenotype from their native state to an osteoblast-like cell. The conversion can be characterized in vitro by downregulation of smooth muscle cell-specific genes and upregulation of transcription factors such as core-binding factor-1 and by bone-specific genes, such as alkaline phosphatase, osteocalcin, and osteopontin.22

A number of manipulations can promote this transition in vitro, but among the most potent stimuli is exposure of the smooth muscle cell to elevated phosphate concentrations.23 The proposed mechanism involves an increase in extracellular phosphorus, promoting an enhanced uptake of extracellular calcium and a stimulus for phenotype change coupled with physicochemical conditions that promote calcification.22,24 The conversion to an osteochondrogenic phenotype is proposed to occur as an adaptation to mineralization of the cytosol and thus further promote formation of vascular lesions that mimic bone.23

The primacy of risk associated with hyperphosphatemia would seem to be supported by epidemiologic data from a broad range of clinical venues. In a review of factors associated with survival of a large cohort of patients undergoing hemodialysis, Block et al determined that patients with the highest serum phosphorus concentrations carried nearly twice the mortality risk compared with patients with normal serum phosphorus concentrations. The apparent risk associated with hyperphosphatemia was extended in an observational study from the Veterans Administration Healthcare System, in which patients with predialysis CKD and elevated serum phosphorus concentrations carried a greater mortality rate than those with lower serum phosphorus levels.7 Furthermore, a post-hoc analysis of the Cholesterol and Recurrent Events study was recently reported, in which survival of a group of patients after myocardial infarction was analyzed.8 In these patients, who by definition had relatively well-preserved GFR, the likelihood of a fatal or nonfatal cardiac event in follow-up was correlated with serum phosphorus concentration. The apparent risk associated with higher serum phosphorus persisted after adjusting for GFR.8

However, several other types of investigation suggest that hyperphosphatemia does not participate alone to cause clinical evidence of arterial calcification. In older observations of a cohort of Pima Indians, medial calcification occurred in the apparent absence of either CKD or elevated serum phosphorus levels.25 More recently, it has become clear that a variety of exposures, including oxidative stress, expression of bone morphogenic proteins, and treatment with serum from human subjects with CKD, induce the phenotypic change of vascular smooth muscle cells to osteochondrocyte-like cells.26,27 In addition, it has been extremely difficult to create an animal model of arterial calcification, even when uremic animals develop elevated phosphorus concentrations in serum.24,28

Vessel calcification likely depends on complex interplay of several critical environmental variables (Figure 5).29 For example, loss of circulating inhibitors of calcification, such as fetuin A, may be an important variable in CKD. Systemic inflammation may create changes that induce bone formation independent of CKD or other clinical factors. It is evident that hyperphosphatemia is not the only risk factor for cardiovascular calcification, but it may be one of the most important variables that a clinician can currently influence.

Figure 5. Complex Interplay of Factors that May Affect Vascular Calcification in Patients with Chronic Kidney Disease

MGP = matrix Gla protein; OPG = osteoprotegrin; OPN = osteopontin; VC = vascular calcification; VSMC = vascular smooth muscle cells. Reprinted with permission from Dellegrottaglie et al. Cardiol Clin. 2005;23:373-384.29
CONCLUSIONS

Disordered mineral metabolism associated with renal dysfunction results in renal osteodystrophy. In addition, elevated serum phosphate levels are independent risk factors for mortality and cardiovascular events in patients with CKD. Extensive vascular calcifications that are morphologically different from those occurring in atheroma increase arterial stiffness in many patients with ESRD. These vascular changes may be among the CKD-specific factors that predispose these patients to elevated cardiovascular risk. However, indications are that the process of underlying vascular calcification begins much earlier and is not simply a physicochemical process. Evidence now suggests that vascular calcification is a dynamically regulated process and that phosphate regulates and coordinates cell signaling and gene expression by dynamic transport processes.

REFERENCES


