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PERSPECTIVES IN RENAL MEDICINE

Pathogenesis of vascular calcification in chronic kidney disease

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Pathogenesis of vascular calcification in chronic kidney disease.

Background. Hyperphosphatemia and hypercalcemia are independent risk factors for higher incidence of cardiovascular events in patients with chronic kidney disease. In addition to increased calcium-phosphate product, hyperphosphatemia accelerates the progression of secondary hyperparathyroidism with the concomitant bone loss, possibly linked to vascular calcium-phosphate precipitation.

Results. The control of serum phosphate levels reduces vascular calcification not only by decreasing the degree of secondary hyperparathyroidism and calcium-phosphate product, but also by reducing the expression of proteins responsible for active bone mineral deposition in cells of the vasculature. The calcium and aluminum-free phosphate-binders provide a new and effective therapeutic tool in preventing vascular calcifications in chronic kidney disease in animal models and in hemodialysis patients.

Conclusion. Additional investigations are necessary to examine the benefits of different phosphate-binders in reducing mortality from cardiovascular disease.

Cardiovascular events are the most frequent cause of death in patients with chronic renal failure [1, 2]. Calcification of soft tissues and blood vessel walls occurs more frequently in dialyzed patients compared to the nonuremic population [3–5].

In the last decade, large evidence has been accumulated indicating that disturbances in mineral and bone metabolism in patients with chronic kidney disease (CKD) associate with vascular calcification and increased morbidity and mortality. Abnormalities in mineral and bone metabolism are very common in end-stage renal disease (ESRD). In this patient population, parathyroid gland enlargement and high circulating levels of parathyroid hormone (PTH) are major contributors to increased bone resorption, a feature of renal osteodystrophy [6, 7]. Thus, vascular calcification is linked to enhanced bone resorption. In addition, an inverse relationship between arterial calcification and bone density has been documented in uremic patients [8]. In the general population there is an association between osteoporosis and vascular calcification [9].

Recently [10], a multivariate analysis performed in a group of patients maintained on hemodialysis demonstrated that the arterial calcification score was positively associated with age and daily dose of calcium-containing phosphate binders, and an inverse correlation with osteoblastic surfaces. A high arterial calcification score was associated with bone histomorphometry suggestive of low bone activity and adynamic bone disease. Thus, an oversuppression of PTH could also influence the development of vascular calcification.

Vascular calcification involves not only passive calcium-phosphate deposition on atherosclerotic vessels but active "ossification" of vascular structures [11, 12]. Hyperphosphatemia and increased calcium-phosphate product are important contributors to vascular calcifications in uremic patients, and also appear to be associated with increased mortality [13, 14]. In particular, elevated blood levels of phosphate associate with ectopic calcifications and increased risk of calciphylaxis [8, 15–17]. Unfortunately, the pathogenic mechanisms for hyperphosphatemia, high calcium-phosphate product, secondary hyperparathyroidism, or kidney disease in itself in enhancing vascular calcification in CKD are still incompletely understood. Because vascular calcifications cause higher morbidity and mortality, the control of serum phosphate in patients with CKD is crucial in preventing increases in calcium-phosphate product, secondary hyperparathyroidism and, therefore, ectopic calcifications [18]. In the past, the standard treatment for the hyperphosphatemia of CKD consisted of dietary phosphate restriction, efficient dialysis treatment, and administration of phosphate-binders (aluminum salts, calcium carbonate, or acetate). Recent studies proved the limitations of calcium salts as phosphate-binders elevating calcium load in patients with ESRD [19, 20], and with more than 50% of patients not achieving a good control of serum phosphate levels [13, 14].

Key words: vascular calcifications, hyperphosphatemia, kidney disease, calcium load, phosphate binders.

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Table 1. Opposite effects of proteins associated with vascular calcification

Inhibitory genes	Inducing genes
Osteopontin (OPN)	Alkaline phosphatase (ALP)
Matrix Gla-protein (MGP)	Osteocalcin (OC)
Fetuin (Ahsg)	Osteonectin (ON)
Osteoprotegerin (OPG)	Bone matrix protein 2a (BMP 2a)

The development of new phosphate binders that do not contain aluminum or calcium opened new perspectives in preventing vascular calcifications in ESRD in animals and humans [20, 21].

This review presents the current understanding of pathogenic mechanisms for regulation and prevention of ectopic calcification in CKD.

PROTEINS MODULATING ECTOPIC CALCIFICATIONS

In the last decade, several studies have defined calcification of atherosclerotic lesions as an active process similar to bone formation. Different gene products seem to induce or inhibit the process of ectopic calcification (Table 1). In particular, matrix Gla-protein, fetuin, osteoprotegerin, and osteopontin may play a very important role on inhibiting mineral deposition in the vasculature. In fact, these 4 "protective" proteins associate with reduced vascular calcification and may be the regulatory keys in preventing ectopic calcification in renal failure.

Matrix gla-protein (MGP)

During the first 8 weeks of life, mice lacking MGP develop osteoporosis and pathologic fractures, as well as diffuse arterial calcification [22]. In addition, MGP is an extracellular matrix protein with high affinity for hydroxyapatite that actively participates in the pathophysiology of osteoporosis and in the prevention of vascular calcification [23]. These data indicate that MGP is required to both promote normal bone formation and inhibit vascular calcification, but its potential role in CKD still needs to be clarified.

Fetuin (Ahsg)

α2-Heremans-Schmid glycoprotein (Ahsg), also known as fetuin-A, is an important inhibitor of ectopic calcification. Serum concentrations of fetuin fall during the cellular immunity-phase of inflammation [24, 25]. In vitro, fetuin inhibits the de novo formation and precipitation of calcium-phosphate, with no effects on hydroxyapatite once it is formed [26, 27]. Ahsg-deficient mice develop extensive soft tissue calcifications in myocardium, kidney, lung, tongue, and skin [28]. Recently, Ketteler et al [29] reported that low serum fetuin levels associate with increased cardiovascular mortality in patients receiving hemodialysis treatment, therefore suggesting that Ahsg could be involved in preventing the accelerated extraskeletal calcification observed in CKD.

Fetuin/MGP complex

In the last 5 years, Price et al [30–33] characterized biochemically and physiologically a high-molecular-mass complex of bone calcium-phosphate mineral and serum fetuin, matrix Gla protein (MGP), and a new 24-kD protein (spp 24), similar to fetuin and MGP [32]. This high-molecular-mass complex inhibits bone mineralization in vivo [30–32].

Paradoxically, in studies stimulating bone resorption with pharmacologic doses of vitamin D [33], formation of fetuin-mineral complex coincides temporally with increases in bone resorptive activity and arterial calcifications. Furthermore, there is a reduction in serum fetuin in rats with ongoing artery calcification. It is possible that excessive bone resorption generates such massive amounts of fetuin mineral complex that impair fetuin ability to further arrest the growth of the mineral components, which could then induce arterial calcifications. The reduction in serum fetuin associates with clearance of the complex from circulation. In fact, when bone resorption is prevented through administration of biphosphonates, there is no reduction of serum fetuin. The striking correlation between depletion of serum fetuin and death suggests that exhaustion of serum fetuin is an important pathophysiologic factor [33].

Osteoprotegerin (OPG)

Bucay et al [34] showed low bone density and increased arterial calcification in OPG-deficient mice. Similar to matrix Gla-protein and fetuin, osteoprotegerin appears to inhibit ectopic calcification, playing an important role in both pathologic and physiologic calcification processes [35].

Osteopontin (OPN)

Recently, several authors [36, 37] proposed that OPN acts as an inhibitor of calcification of vascular smooth muscle cell (VSMC) cultures, while Jono et al [38] demonstrated that the phosphorylation of osteopontin was a mandatory step to inhibit VSMC calcification. Thus, osteopontin is both an important modulator of bone mineralization and a potent inhibitor of ectopic calcifications.

In contrast to the protective effects of matrix Gla-protein, fetuin, osteoprotegerin, and osteopontin, a higher expression of osteocalcin, alkaline phosphatase [39], osteonectin [40], and BMP2a [41] was associated with myofibroblasts and vascular smooth muscle cells being diverted to the osteogenic lineage with a concomitant