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The bone-vascular axis in chronic kidney disease

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Abstract

PURPOSE—This review highlights the most recent publications addressing the relationship between bone and vascular calcification in patients with chronic and end-stage kidney disease.

RECENT FINDINGS—The relatively new term “chronic kidney disease - mineral bone disorder” (CKD-MBD) reflects the growing reach of CKD research into the realm of systems physiology, involving a triad of renal, skeletal and vascular tissues. Recent studies address underlying mechanisms of the bone and vascular complications of CKD and point to a variety of biochemical factors, including phosphatonins [fibroblast growth factor-23, matrix-matrix extracellular phosphoglycoprotein], bone morphogenetic protein 7, osteoprotegerin, matrix GLA protein, ectonucleotide pyrophophatase/phosphodiesterase 1, alkaline phosphatase, and lipid oxidation products. Studies also demonstrate that agents used for treatment of one component of the triad often act on the other components of the triad - beneficially or adversely. These findings emphasize the importance of avoiding the subspecialty, single organ viewpoint when treating individual components of CKD-MBD.

SUMMARY—The consistent synchrony among chronic kidney disease, aortic calcification and bone loss offers clues to underlying mechanisms for the systemic abnormalities.

Keywords

Calcification; Vascular; Osteodystrophy; Kidney

Introduction

In patients with chronic kidney disease (CKD), cardiovascular mineralization co-exists paradoxically with skeletal demineralization [1-3]. Over half of CKD patients have some form of cardiovascular calcification even before undergoing dialysis [4]. Towler has described CKD as the “perfect storm” for cardiovascular calcification [5]. This association is increasingly recognized among nephrologists, as evidenced by the formal acceptance of the term “chronic kidney disease-mineral [and] bone disorder (CKD-MBD)” to describe the systemic disorder that includes soft tissue calcification as well as disordered mineral metabolism and skeletal bone growth, volume, turnover, mineralization, and/or strength. Previously, the skeletal abnormalities of CKD were considered in isolation as “renal osteodystrophy.” The broader clinical syndrome, CKD-MBD, formalized in 2005 at the Controversies Conference on Renal Osteodystrophy organized by Kidney Disease: Improving Global Outcomes [6], acknowledges the systemic consequences and damage to organs beyond bone, primarily cardiovascular calcification. In this review, we focus on reports published in 2009-10 that address the bone-vascular axis in chronic kidney disease,

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that is, how the cardiovascular calcification and bone disorders are linked in CKD-MBD patients.

Clinical aspects of CKD-MBD are under investigation by a number of groups, including Moe and colleagues [7] and London and colleagues [8]. In patients with CKD-MBD, cardiovascular mineralization predominantly forms within the *tunica media* or medial layer of conduit and muscular vessels, termed medial calcification. It often arises along the sheets of elastin. Even calcification of intimal atherosclerotic plaques and cardiac valves, particularly the aortic valve and mitral annular ring, may, and often does, arise concurrently with medial calcification.

Although Shroff and colleagues found that vessels from both predialysis and dialysis patients have significantly more calcium content than vessels from control patients, it is the dialysis patients who develop increased aortic stiffness [9], raising questions about possible differences in the quantity and mechanical quality of calcium deposits under the two circumstances. They also reported that only dialysis patients have extensive loss, through apoptosis, of smooth muscle cells (SMC) [9]. Resulting apoptotic bodies, which resemble matrix vesicles, may provide the nidus for initiation of hydroxyapatite crystal formation.

Whether renal disease contributes to aortic stiffness was addressed by Kis and colleagues [10], who found that children with CKD, who received renal transplant, had lower aortic stiffness than those on dialysis, suggesting that dialysis promotes aortic stiffness, presumably due to aortic calcification.

Calcium deposition imparts the greatest mechanical stiffness to arteries compared with collagen and elastin. Aortic calcification is positively associated with calcium load and negatively associated with bone activity. Adynamic bone is independently associated with greater aortic stiffness regardless of calcium load [11]. In the presence of adynamic bone disease, calcium load (phosphate binders) has a significantly greater influence on aortic calcification and stiffening [11].

Prior studies have identified a direct role of inflammation in CKD and its cardiovascular complications. However, it is not known whether the same cytokines drive both. Barreto and colleagues [12] showed that at least one key inflammatory mediator, interleukin-6 (IL-6), corresponded with CKD severity and was a strong predictor of cardiovascular mortality in patients at various stages of CKD. Interestingly, the authors also found that IL-6 levels did not correlate with severity of aortic calcification or stiffness [12], suggesting, among many possibilities, that different cytokines mediate vascular calcification, or that the inflammatory stimuli for the two disorders are not simultaneous.

It is not clear which aspect or aspects of bone pathology associate with vascular calcification in hemodialysis patients. Tomiyama and colleagues [4] found an association of vascular calcification with bone density, volume, and formation rate, but Adragao and colleagues [13] found the association limited to bone volume, not formation rate, based on a small cross-sectional study of hemodialysis patients.

Experimental animal models

Previously, rodent models used for CKD were the 5/6th nephrectomy and the adenine diet models. These models have both vascular and bone disorders representative of acute onset kidney injury with rapidly developing hyperphosphatemia and hyperparathyroidism. Recently, Moe and colleagues [14] developed a rat model of slowly progressive CKD, a Cy/+ rat with autosomal dominant polycystic kidney disease, which spontaneously develops gradual CKD-MBD with vascular calcification on a normal phosphate diet.

Potential mechanisms

It remains controversial whether the association between vascular calcification and bone disorders in CKD is attributable to a causal relationship between the two or a shared cause, such as aging or obesity. With respect to the role of aging, Tomiyama and colleagues recently found that the relationship between coronary calcification and low bone formation rate occurs independently of age in CKD patients not on dialysis [4]. It has generally been considered that obesity correlates with high bone density due to higher mechanical load on bones due to weight alone. Recent studies indicate that, when corrected for lean mass, obesity is actually a risk factor for osteoporosis [15]. More specifically, the recent work of Benetos and colleagues [16] found that aortic stiffness correlates with fat mass but not lean mass; conversely bone density correlates with lean mass but not fat mass. These findings suggest that there are independent regulatory mechanisms by which body composition governs vascular vs. skeletal mineralization.

To address whether bone loss fuels vascular calcification, Barreto and colleagues [17] recently confirmed the inverse relationship between bone volume and coronary calcification in hemodialysis patients. As further evidence that the bone disorder contributes to vascular calcification, Skolnik and colleagues [18] performed a small observational study comparing osteoporosis treatment (bisphosphonates, calcitonin, or estrogen receptor modulators) with echocardiographic progression of calcific aortic stenosis. They found that osteoporosis treatment was strongly associated with decreased progression of calcific aortic valve stenosis [18]. Notably, the latter study excluded patients with CKD, and, as an observational study, it leaves the possibility that patients, who sought and complied with osteoporosis treatment, also sought and complied with “heart-healthy” regimens that independently reduced valve disease progression.

Other findings suggest that bone anabolic agents reduce vascular calcification in CKD. Previously, the Towler laboratory demonstrated that intermittent parathyroid hormone (PTH) regimen, an anabolic bone treatment for osteoporotic patients, attenuates vascular calcification in mice [19]. Sebastian and colleagues [20] have now corroborated their findings in a rat model of renal failure, and further demonstrated that intermittent PTH also protects against nephrectomy (NPX)-induced vascular calcification. Interestingly, in the untreated rats, vascular calcification did not develop in animals that underwent both nephrectomy and parathyroidectomy despite similar serum levels of Pi and of bone parameters as NPX-only rats [20].

Regulatory factors

During the period covered by this review, investigators have advanced knowledge about the biochemical factors that regulate the bone-vascular axis in CKD, including phosphatonins [fibroblast growth factor-23 (FGF-23), matrix-matrix extracellular phosphoglycoprotein (MEPE)], bone morphogenetic protein 7 (BMP-7), osteoprotegerin (OPG), matrix GLA protein (MGP), ectonucleotide pyrophophatase/phosphodiesterase 1 (Enpp1), bone/liver/kidney (“tissue non-specific”) alkaline phosphatase (TNAP), and lipid oxidation products.

FGF-23, a phosphatonin secreted by osteoblasts to regulate kidney excretion of phosphate, is highest in patients who have received long-term hemodialysis, and among these patients, the serum level of FGF-23 correlates with vascular calcification and mortality [21]. Nasrallah and colleagues [22] confirmed that FGF-23 and aortic calcification index were significantly increased in dialysis patients and further showed that the severity of aortic calcification correlated significantly and independently with FGF-23, based on stepwise multiple regression analysis, as did systolic blood pressure; the two parameters explaining approximately 50% of the variance in aortic calcification. El-Abbadi and colleagues also

found a correlation of aortic calcification with FGF-23 as well as with osteopontin [23]. In the latter study, a high phosphate diet was found to cause hyperphosphatemia, but not hypocalcaemia, and to cause extensive aortic medial calcification in uremic, though not in normal, mice [23], indicating that normal renal function is required to respond to FGF-23 to regulate phosphate metabolism. Another phosphatonin, matrix-matrix extracellular phosphoglycoprotein (MEPE), may also regulate bone and soft tissue calcification; mice overexpressing MEPE have reduced bone mineralization and are resistant to diet-induced renal calcification [24].

In most cases, there is a reciprocal relationship between bone and vascular calcification. Possible common etiological factors that may account for the association between the vascular calcification and skeletal decalcification include – BMP-7 and products of lipid oxidation caused by oxidative stress. BMP-7 has been studied extensively by the Hruska laboratory [25]. The Diabetes Heart Study showed that single nucleotide polymorphisms in the BMP-7 gene had statistically significant (and reciprocal) effects on vascular calcification and bone density in a population enriched with diabetes [26]. Lipid oxidation products also may cause both vascular mineralization and skeletal demineralization [27,28]. Their role in atherosclerosis and vascular calcification is established, and their contribution to bone disease is under active investigation. Graham et al. [29] recently found that oxidized lipids enhance T lymphocyte production of the ligand for receptor activator of nuclear factor-kappa B (RANKL), which activates osteoclastic differentiation, suggesting a role for oxidized lipids in bone resorption.

Paradoxically, OPG, a soluble decoy receptor for RANKL, has been associated with coronary artery disease and vascular calcification [30]. In the Dallas Heart Study of a large general population, elevated serum OPG levels were associated with greater coronary calcification [31]. Morena and colleagues [32] found that plasma OPG levels greater than 750 pg/mL may predict coronary calcification in CKD patients. Interestingly, Morony and colleagues [33] showed that OPG treatment in *Ldlr*$^{-/-}$ mice attenuates vascular calcification without affecting the area of atherosclerotic lesions. These studies suggest that OPG may associate with vascular calcification as a mitigating factor, rather than a causal one.

Extracellular pyrophosphate plays a key role in inhibiting mineralization at the level of nanocrystal formation in both bone and vasculature. In seminal work, Terkeltaub and colleagues [34,35] discovered the gene defect, mutation in Enpp1, causing the lethal congenital disorder “idiopathic infantile arterial calcification,” which is now known as “generalized arterial calcification of infancy.” The mechanism was identified as deficiency of pyrophosphate generation by Enpp1. A new report from Babij and colleagues [36] identifies strains of mice with spontaneous mutations in Enpp1 that have phenotypes of low bone mass and ectopic calcification in the heart, aorta, and renal arteries and capillaries. In CKD patients, TNAP, which degrades pyrophosphate, is associated with risk factors for vascular calcification. CKD severity, TNAP, and the bone resorption marker, tartrate resistant acid phosphatase, predict cardiovascular events [37]. However, it is not clear whether loss of pyrophosphate generation by Enpp1 or excess breakdown of pyrophosphate by alkaline phosphatase have a role in the vascular and bone complications of CKD.

Pharmacological agents

Many hemodialysis patients require life-long anticoagulation treatment, usually with warfarin, to prevent thrombosis of their vascular shunts. Interestingly, warfarin’s anticoagulant activity is based on its inhibition of vitamin K-dependent gamma-carboxylation of glutamic acid residues in proteins of the classical coagulation cascade. Coagulation proteins and Gas-6 are the only other proteins besides the two bone-related

proteins, MGP and osteocalcin (also known as bone GLA protein; BGP), that require vitamin K-dependent gamma-carboxylation. Presumably, the connection is the shared requirement for calcium binding. Thus, warfarin treatment of rodents is an established model for vascular calcification [38]. Recently, warfarin was shown to reduce lumbar spine bone density in children [39]. Based on its inhibitory effect on MGP activity, warfarin is expected to induce cardiovascular mineralization. In a recent study of almost 200 patients, Koos and colleagues [40] found that calcific aortic stenosis increased with reduced level of uncarboxylated MGP levels. Interestingly they also reported that renal dysfunction also reduced uncarboxylated MGP levels. In mouse studies, warfarin induced aortic calcification and reduced expression of MGP in aortic tissue and significantly increased cardiac valve calcification [40].

Therapeutic agents for atherosclerosis, HMG-CoA reductase inhibitors (“statins”), are reported to have pleiotrophic effects, including functioning as a vitamin D analog. In a recent retrospective analysis of CKD patients who were using statins, Ashman and colleagues found that the statins failed to substitute for vitamin D in control of PTH levels [41].

Therapeutic agents for osteoporosis and hyperparathyroidism also may influence both vascular and bone mineralization in CKD. Recently, Lomashvili and colleagues [42] found that, in mice with adenine diet-induced uremia, bisphosphonates inhibited aortic calcification. This model was unusual in that uremic rats had higher bone formation rate compared with non-uremic rats and that bisphosphonate treatment reduced bone formation rate in uremic rats, returning it to the level of non-uremic controls [42]. In the Cy/+ rat model [43] the calcimimetic R-568 lowered serum PTH and calcium levels but raised phosphate levels. R-568 with calcium supplements yielded more dramatic improvements in bone volume, but produced more extraskeletal calcification than R-568 alone [43]. Overall, this example and others make it clear that treatment of one aspect of CKD-MBD may lead to undesirable effects on others.

Conclusion

In summary, there are shared mechanisms and regulatory factors governing vascular, bone, and renal systems. Therefore, phosphate and hormonal dysregulation caused by chronic kidney disease promote the disorders of vascular and skeletal biomineralization. The interplay between these organs underscores the importance of systems physiology research and a systems view in treating these diseases.

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