Mechanisms Linking Osteoporosis With Cardiovascular Calcification

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Cardiovascular calcium deposition is associated with osteoporosis through various potential mechanisms involving molecular regulatory factors at the nanoscale level that govern skeletal bone and cardiovascular tissues. In this article, several possible mechanisms linking cardiovascular calcification and osteoporosis are discussed, including aging, tissue-specific responses to chronic inflammation, flow-limiting atherosclerosis of skeletal end arteries causing ischemic abnormalities in metabolism, shared endogenous regulatory factors that affect the two tissues in a reciprocal manner, and changes in a cysteine protease inhibitor, fetuin. Any or all of these factors and phenomena may contribute to the association.

Introduction

Cardiovascular calcification is a widespread disorder that affects the majority of individuals over 60 years of age. Surprisingly, it is more common in patients with osteoporosis. Many studies suggest that this effect is independent of age. The calcium deposits in arteries and heart valves often consist of fully formed bone tissue, including trabeculae and marrow. Thus, patients who are losing bone from their skeleton are simultaneously producing bone in their arteries. It is not known whether aortic calcification is a direct or indirect effect of bone loss or shares a common cause with it. Nevertheless, if the relationship is age independent, it raises important questions about whether dietary calcium could truly represent a limiting factor in osteoporosis and whether treatments for osteoporosis may simultaneously affect cardiovascular calcification.

Calcium deposits arise in many anatomic locations in the cardiovascular tree, and their growth is accelerated by certain metabolic conditions, including atherosclerosis, diabetes, and chronic kidney disease. They are most common in the aorta, coronary arteries, cardiac valves, and peripheral arteries. The most extensive cases are in patients with renal failure, which, as Towler and Vattikuti [1,2] have noted, have a combination of features creating a "perfect storm" for vascular calcification. Most vascular calcium deposits appear amorphous, but in atherosclerotic plaque and cardiac valves, they also contain fully formed bone tissue. Calcium deposits associated with atherosclerosis are located in the neointima, whereas those associated with renal failure are prominent in the medial layer. The two layers may be affected simultaneously, as is often seen in diabetes.

The clinical significance of calcific vasculopathy depends on its location. In the aorta, it greatly increases stiffness, thus impairing cardiac function and hemodynamics and promoting systolic hypertension. Aortic calcification correlates with risk of myocardial infarction and stroke, even after adjusting for age, lipoproteins, triglycerides, blood pressure, smoking, renal function, health status, and baseline diagnoses of diabetes mellitus, hypertension, angina, and prior stroke [3]. In coronary and carotid arteries, it serves as a marker for subclinical atherosclerosis. In the peripheral arteries, it associates with greater ischemia, and it is a better predictor for lower extremity amputation than ankle-brachial index and traditional risk factors. In microvessels of the extremities, where it is known as calcific uremic arteriolopathy, tissues downstream of the calcified microvessels infarct, leading to necrosis and autoamputation [4]. In the cardiac leaflets, it causes valvular stenosis and regurgitation. Overall, calcium deposition has a profound impact on cardiovascular function.

Plaque Vulnerability

Calcium deposits also have local effects within atherosclerotic plaque of the intimal layer. Plaque rupture is considered the initiating event in most cases of coronary thrombosis and myocardial infarction. Theoretical analyses of mechanical stress using finite element modeling indicate that calcium deposits within atherosclerotic plaque affect the vulnerability of plaque to rupture, depending on their location relative to lipid deposits [5] and their proximity to the lumen, where shear stress comes into play [6]. Experimental evidence is sparse because models are limited; however, Lin et al. [7] recently established a novel cell culture model for rupture of calcified plaque under shear stress.

Nanoscale Factors

Skeletal and vascular biomineralization share features not only at the cellular level but also at the nanoscale level. Matrix vesicles are nanovesicles generated by osteoblasts that appear to provide a nidus for hydroxyapatite crystal initiation in cartilage matrix mineralization. They also are enriched in certain active enzymes, including alkaline phosphatase and nucleotide pyrophosphatase/phosphodiesterase 1 (NPP1), and are found in human atherosclerotic plaque and in cultured human and bovine vascular smooth muscle cells (VSMCs). Chen et al. [8] recently showed that when VSMCs are treated with osteogenic medium (containing inorganic phosphate or β-glycerophosphate), their matrix vesicles have greater alkaline phosphatase activity but less fetuin, and they mineralize when plated on type I collagen but not on type II collagen.

Additional nanoscale similarities were recently observed by Duer et al. [9•]. Using solid-state nuclear magnetic resonance technique, they found that in both tissues the mineral-organic interface is a bonded nanocomposite rather than a simple mixture and that it is enriched in glycosaminoglycans, a major component of cartilage matrix.

Epidemiologic Association Between Cardiovascular Calcification and Osteoporosis

Several reports show an inverse relationship between vascular calcification and bone mineral density (BMD) [10]. In many but not all studies, this relationship is independent of age. In a study of about 3000 healthy postmenopausal women, aortic calcification measured by conventional lateral radiography was associated with diminished bone density in the proximal femur. Importantly, the severity of aortic calcification was an independent predictor of hip fractures, low bone density, and accelerated bone loss in the femur [11]. In postmenopausal women, increased bone density was associated with significantly lower odds of having coronary artery calcification, independent of age, fat-free mass, high-density lipoprotein cholesterol, current smoking, and use of cholesterol-lowering medications. To determine whether coronary artery disease itself, as opposed to coronary calcification, correlates with low bone density, Tekin et al. [12] measured BMD in patients undergoing coronary angiography. Their results showed that coronary stenotic narrowing, irrespective of calcification, was significantly more prevalent among women with low bone density.

In some studies, the inverse relationship with BMD was not age independent for all types of vascular calcification. In healthy, middle-aged women, the inverse association between aortic calcification and vertebral BMD was found to be age independent, but the inverse association of coronary artery calcification with BMD was not [13]. To control for genetic confounders, Shen et al. [14] studied Amish men and women and found that coronary artery calcification or aortic calcification was not associated with lower femoral BMD, although a history of cardiovascular disease was correlated with low BMD. In a study of about 300 postmenopausal women, Sinnott et al. [15] also found a significant inverse association between coronary calcification score and lumbar vertebral bone density, but it was not independent of age.

In dialysis patients, low femoral but not lumbar spine bone density was associated with greater aortic stiffness measured by higher pulse wave velocity as well as more extensive vascular calcification and peripheral artery disease [16]. Even in predialysis renal patients, vascular calcification increases rapidly with age, hypertriglyceridemia, and reduced renal function. In these patients, femoral bone density is significantly inversely associated with vascular calcification [10].

Potential Mechanisms Linking Coronary Calcification With Osteoporosis

One possible mechanism for a relationship between coronary calcification and osteoporosis is that the two processes are tissue-specific responses to chronic inflammation. It is clinically well known that osteolysis and lytic changes accompany inflammation, osteomyelitis, and arthritides. Al-Aly et al. [17••] and Cheng et al. [18••] have provided compelling evidence that the inflammatory cytokine tumor necrosis factor-α potently regulates osteochondrogenic differentiation in osteoblastic and vascular cells through Msx2 and Wnt signaling pathways, based on in vitro and in vivo models. These investigators also demonstrated the importance of these signaling pathways in mediating effects of osteopontin, oxidant stress, and bone morphogenetic proteins on biomineralization [19].

The inflammatory nature of vascular mineralization was dramatically demonstrated by Aikawa et al. [20] using innovative imaging technologies in mice. In atherosclerosis, inflammation results from deposition and oxidation of lipids in the subendothelial space. Lipid deposits are also found in osteoporotic bone tissue, in the subendothelial spaces within the haversian canals [21]. Brodeur et al. [22] have shown adverse effects of oxidized lipids on osteoblasts as well as evidence that osteoblasts mediate lipid oxidation, strongly suggesting increased local concentrations of oxidized lipids in bone tissue. Compared with wild-type C57BL/6 mice, genetically hyperlipidemic apoE$^{-/-}$ mice fed a high-fat diet have significant reductions in the volume, thickness, and formation rate of cortical bone [23]. The lipids not only inhibit spontaneous osteoblast mineralization but they also attenuate osteoblastic differentiation induced by osteogenic agents such as parathyroid hormone (PTH) and bone morphogenetic protein-2 [24]. In vivo findings suggest that oxidized lipids interfere with anabolic effects of PTH [25•], raising the question of whether osteoporosis treatment would be beneficial in chronically hyperlipidemic patients. Interestingly, intermittent

PTH treatment ameliorated aortic calcification in an experimental model of renal failure [26,27].

An alternative mechanism for the association between calcific atherosclerosis and osteoporosis, suggested by Bagger et al. [28], is flow-limiting atherosclerosis of skeletal end arteries, causing metabolic abnormalities due to hypoperfusion. These investigators studied more than 1000 elderly women and found that coronary calcification severity was significantly inversely associated with vertebral BMD but that lipid profile parameters did not correlate with bone parameters, including spine and hip BMD. Although some of the subjects were taking lipid-lowering drugs, which could mask an association, the study raises the important possibility that the correlation may not be attributable to lipid metabolic abnormalities affecting both tissues, but rather to atherosclerotic disease of arteries supplying bone tissue.

Another potential mechanism for the inverse relationship between coronary calcification and osteoporosis is a shared endogenous regulatory factor that affects the two tissues in a reciprocal manner. Skeletal bone and vascular tissue have many osteogenic regulatory molecules in common. One such factor, transglutaminase 2, was previously known to mediate differentiation of osteoblasts [29]. Recently, Johnson et al. [30•] demonstrated that it has an important role in vascular calcification. Transglutaminase 2 modulates tissue repair by transamidation-catalyzed covalent cross-linking of extracellular matrix proteins. This investigative group showed that its release is critical for chondro-osseous differentiation and matrix mineralization in smooth muscle cells, whether induced by inorganic phosphate supplementation or bone morphogenetic protein-2 [30•].

Other bone regulatory factors also associate with cardiovascular calcification. Some soluble factors produced by bone cells may be released into the circulation, and some may be produced directly by vascular cells. For example, in patients, levels of osteoprotegerin (OPG), an inhibitor of bone resorption, positively associates with clinical coronary calcification [31] and aortic stiffness [32], suggesting an adverse effect of OPG on the vasculature. However, in mice, OPG deficiency is associated with aortic calcification [33], suggesting a protective role. Similarly, in hyperlipidemic mice, OPG deficiency worsens atherosclerosis progression and calcification [34•], and recombinant OPG treatment of hyperlipidemic mice reduces aortic calcification without affecting atherosclerosis severity [35]. Using a different mouse model of OPG deficiency developed in mice of a different background strain, Orita et al. [36] found that aortic calcification requires a high-phosphate diet and vitamin D treatment, conditions similar to those in patients with renal insufficiency. As further evidence of complexity, OPG production in cultured vascular cells has a biphasic response during osteogenic differentiation induced by exposure to cytokines such as interleukin-4, showing an increase in OPG with short-term exposure and a decrease in OPG with long-term exposure [37]. Though it is an attractive possibility that OPG and its ligand RANKL (receptor activator of nuclear factor-κB ligand) mediate the association between coronary calcification and BMD, in at least one study of postmenopausal women using estrogen, neither OPG nor RANKL serum levels were significant effect modifiers of the vascular–bone relationship after adjustment for age and other risk factors [38]. Altogether, these findings indicate a complex relationship between serum OPG regulation and cardiovascular calcification.

Another serum factor that may link vascular with bone metabolism is the cysteine protease inhibitor, fetuin. Serum fetuin levels correlate with intima-media thickness, a measure of atherosclerosis, but correlate inversely with the osteogenic differentiation marker, alkaline phosphatase, and vertebral and femoral bone mass [39].

Osteophytes and Aortic Calcification

Soft tissue calcification also comes in the interesting form of osteophytes, outgrowths of bone into neighboring soft tissue such as the ligament anterior to the lumbar vertebrae. Karasik et al. [40] showed that lumbar osteophytes are significantly associated with abdominal aortic calcification independent of age, sex, body mass index, smoking, alcohol consumption, physical activity, systolic blood pressure, total cholesterol level, diabetes, and estrogen replacement therapy. In this location, osteophytes and abdominal aortic calcification may confound BMD measurements based on dual-energy x-ray absorptiometry, because these structures overlie the path of the x-ray beam traversing the lumbar vertebrae. Such an effect may yield false-positive benefits in therapeutic trials if the agents promote calcium deposition in soft tissue.

Ex Vivo and In Vivo Models

A variety of models are available to investigate associations between vascular calcification and osteoporosis, especially in the context of hypervitaminosis and renal insufficiency. Price et al. [41•,42] have described ex vivo and rodent models that provide evidence for a direct role of osteoporosis in artery wall calcification. In a rat model of renal failure induced by an adenine diet, severe abnormalities of calcium metabolism develop rapidly. As in humans with chronic kidney disease and uremia, cortical bone density was reduced and coronary and aortic calcification was increased [43].

Exercise

Fitness and activity appear to benefit both coronary and bone metabolism. Cardiovascular fitness, measured by Vo_2max, showed a significant inverse correlation with coronary calcification in men [44]. In a 15-year follow-up of more than 2000 young adults, physically fit individuals had a lower risk of developing coronary calcification than individuals in poor condition [45]. Similarly, another study found that physical activity was significantly associated with bone formation markers in cross-sectional and longitudinal aspects of the study, including adjustment for age and body weight [46].

Conclusions

Overall, recent findings suggest that coronary calcification is associated with osteoporosis through a variety of potential mechanisms involving molecular regulatory factors that govern both skeletal bone and cardiovascular tissues.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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