Molecular Mechanisms of Vascular Calcification
Lessons Learned From The Aorta
Jian-Su Shao, Jun Cai, Dwight A. Towler

Abstract—Vascular calcification increasingly afflicts our aging and dysmetabolic population. Once considered a passive process, it has emerged as an actively regulated form of calcified tissue metabolism, resembling the mineralization of endochondral and membranous bone. Executive cell types familiar to bone biologists, osteoblasts, chondrocytes, and osteoclasts, are seen in calcifying macrovascular specimens. Lipidaceous matrix vesicles, with biochemical and ultrastructural “signatures” of skeletal matrix vesicles, nucleate vascular mineralization in diabetes, dyslipidemia, and uremia. Skeletal morphogens (bone morphogenetic protein-2 (BMP) and BMP4 and Wnts) divert aortic mesoangioblasts, mural pericytes (calcifying vascular cells), or valve myofibroblasts to osteogenic fates. Paracrine signals provided by these molecules mimic the epithelial–mesenchymal interactions that induce skeletal development. Vascular expression of pro-osteogenic morphogens is entrained to physiological stimuli that promote calcification. Inflammation, shear, oxidative stress, hyperphosphatemia, and elastinolysis provide stimuli that: (1) promote vascular BMP2/4 signaling and matrix remodeling; and (2) compromise vascular defenses that limit calcium deposition, inhibit osteo/chondrogenic trans-differentiation, and enhance matrix vesicle clearance. In this review, we discuss the biology of vascular calcification. We highlight how aortic fibrofatty tissue expansion (adventitia, valve interstitium), the adventitial-medial vasa, vascular matrix, and matrix vesicle metabolism contribute to the regulation of aortic calcium deposition, with greatest emphasis placed on diabetic vascular disease. (Arterioscler Thromb Vasc Biol. 2006;26:000-000.)

Key Words:

With advanced age, vascular inflammation, hypertension, and certain metabolic disorders, calcium accumulates in the arterial macrovasculature. Calculation of aortic valve leaflets and atherosclerotic plaques have long been recognized as clinically important. However, medial artery calcification (MAC) also portends mortality and amputation risk. Studies of vascular calcified tissue metabolism significantly lag behind those of skeletal metabolism. Executive cell types familiar to bone biologists are seen in calcifying aortic specimens. As in bone, endothelial, mesenchymal, and hematopoietic cell lineages control vascular mineral accumulation, with cellular activities entrained to morphogenetic, metabolic, inflammatory, and mechanical demands placed on each vascular segment.

We provide a brief overview of vascular calcification, emphasizing how paracrine osteogenic signals recruited by dysmetabolic insults promote aortic calcium deposition in diabetic vascular disease. We point to emerging evidence that inflammation, mechanical, and metabolic oxidative stresses not only provide stimuli that induce vascular osteogenic morphogens but also compromise defense mechanisms that limit vascular calcium deposition.

Aortic MAC
MAC is a highly characteristic feature of diabetes and chronic kidney disease (CKD). Although diabetes is the major cause of CKD, hyperglycemia conveys independent risk for vascular calcification. Aortic calcium scores, but not coronary calcium scores, are linearly related to fasting blood glucose. MAC has emerged as an exceptionally strong predictor of lower extremity amputation and mortality in patients with type II diabetes. Mechanisms are still unclear but may relate to abnormal aortofemoral Windkessel physiology that generates systolic hypertension, increases myocardial workload, and perturbs normal microvascular tissue perfusion. Aortic pulse wave velocity, an index of vascular stiffness, is highly correlated with the prevalence of aortic calcification and diabetes in CKD. Increases in aortic stiffness convey the impact of diabetes-enhanced cardiovascular mortality. Thus, a better understanding of the mechanisms controlling aortic MAC is required to address the burgeoning unmet clinical needs of diabetic vascular disease and CKD.

In diabetes and CKD, MAC proceeds via matrix vesicle nucleated mineralization, with apatitic calcium phosphate deposition in the tunica media occurring in the absence of

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atheroma and neointima. (Of note, this differs from calcific uremic arteriolopathy, an uncommon disorder in which fibroproliferative occlusion and medial calcification of arterioles cause skin and sometimes intestinal necrosis15). The concentric nature of MAC stands in stark contrast to the eccentric, calcified atherosclerotic plaque.1,16 At least 2 types of lipid vesicles have been identified to date that nucleate vascular calcification: (1) the apoptotic bodies (250-nm diameter) of dead and dying cells; and (2) mineralizing matrix vesicles (100 nm diameter) actively extruded by viable vascular smooth muscle cells (VSMCs) and calcifying vascular cells (CVCs).12–14,17 The latter resembles the mineralization of membranous bone,13,17 is intensely procalcific,14 and appears predominately in aortic calcification.12,14,17

Mechanisms controlling MAC in type II diabetes are beginning to be understood. High-fat diets that induce obesity, insulin-resistant diabetes, and dyslipidemia promote aortic MAC and valve calcification in male low-density lipoprotein receptor (LDLR)–deficient mice.18,19 An aortic bone morphogenetic protein-2 (BMP2)–Msx2 signaling cascade is activated by mural oxidative stress and inflammatory cytokines18,19 (Figure 1). Because Msx2-dependent gene expression is critical for craniofacial bone formation,20 this suggested that similar signals participate in diabetic MAC. Intriguingly, a subset of myofibroblasts in the fibrofatty aortic adventitia and aortic valve interstitium, but not the tunica media, elaborated this early BMP2–Msx2 response.18,19

Emerging evidence indicates that vascular osteogenic signals, initiated by adventitial BMP2–Msx2 actions, are concentrically conveyed to the calcifying tunica media via the vasa vasorum18,19,21,22 (Figure 1). Diabetes causes low-grade adventitial and medial inflammation, with adipocyte-laden expansion and associated mural neoangiogenesis23,24 (Figure 1). Primary vasa, arising from overt branch points in the arterial tree, sprout and meander through the adventitia, then ramify to form secondary vasa that circumferentially penetrate and percolate the aortic tunica media25 (Figure 1). The vasa vasorum is most evident in larger mammals25 and becomes grossly manifest in dyslipidic mice.26,27

What molecules convey vascular osteogenic signals? Recent data from our laboratory19 and the Rajamannan laboratory28 have shown that Wnts are important. Wnts are secreted polypeptides that bind specific LDLR-related protein (LRP)/frizzled heterodimers, activate LRP5- and LRP6- signaling cascades, and augment gene expression via nuclear catenin in the canonical pathway.19,28 Cultured Msx2-expressing mesenchymal cells secrete an osteogenic activity that is antagonized by Dkk1, an inhibitory ligand of LRP5/6 and paracrine Wnt signaling.19 These results were confirmed in vivo using CMV–Msx2 transgenic mice,19 a model validated previously in studies of ectopic calvarial bone formation. Whereas Msx2 accumulates in the aortic adventitia, alkaline phosphatase (ALP) induction occurs in the tunica media with concomitant MAC.19 Importantly, the Msx2 transgene selectively upregulated galactosidase (LacZ) in the tunica media of TOPGAL mice (TCF/LEF optimal promoter-galactosidase reporter mouse; demarcates canonical Wnt actions in vivo).19 The vector of mural microvascular flow is from adventitia to
media (Figure 1); therefore, we posited that paracrine Wnt signals were elaborated by Msx2-expressing cells of the adventitia, and that these Wnt signals programmed concentric mineralization via the CVCs of the tunica media. Surgical stripping of the adventitia significantly reduces MAC in rats fed high-fat diets, consistent with this notion.

How does induction of vascular BMP contribute to activation of this osteogenic signal? In craniofacial osteoblasts, BMP2 is a key stimulus for Msx2 expression and enhances Wnt signaling. Aortic Msx2–Wnt signaling is also stimulated by BMP2 (Figure 2). Intraperitoneal BMP2 administration upregulates aortic Msx2 and canonical Wnt signaling, the latter indicated by the accumulation of LacZ mRNA. Surgical stripping of the adventitia significantly reduces MAC in rats fed high-fat diets, consistent with this notion.

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What are the origins of aortic osteogenic cells and Msx2-expressing adventitial cells? At least 2 aortic mesenchymal cell types can contribute to the ectopic osteogenic programs of vascular calcification: (1) multipotent vascular mesenchymal progenitors that are recruited to form the mural CVCs; and (2) VSMCs that can undergo osteo/chondrogenic transdifferentiation in response to hyperphosphatemia. Demer first described the aortic CVCs. The CVC is a macrovascular myofibroblast subtype related to the microvascular pericyte. Of note, pericytes from multiple vascular beds function as osteoprogenitors in vitro. It is highly probable that CVCs arise from local mesenchymal progenitors recruited during
vascular injury responses. Markers for pericytes and CVCs are few but include 3G5, smooth muscle α-actin, and Stro1 (human). Importantly, an abundant Scal1+ (stem cell antigen) cell population resides within the aortic adventitia in dyslipidemic apolipoprotein E−/− and LDLR−/− (our unpublished data) mice that contributes to medial and intimal injury responses. During vertebrate development, a Scal1+ CD34+ mesenchymal progenitor, the mesoangioblast, resides in the dorsal aorta that is programmed by Msx2. In response to BMP2, mesoangioblasts upregulate ALP and differentiate into mineralizing osteoblasts. Because neoangiogenesis generates bipotential endothelial cell, VSMC progenitors resembling the mesoangioblast model posits that dysmetabolic signals that expand the adventitial vasa simultaneously expand the mural pool of Scal1+ mesenchymal progenitors. In addition, many laboratories have demonstrated that aortic VSMCs can undergo a type of phenotypic modulation: “trans-differentiating” into mineralizing VSMCs that elaborate markers of the osteo/chondrogenic lineage. The hyperphosphatemia of CKD is an important stimulus for this process, signaling through cell surface Na/phosphate cotransporter Pit1/Glvr1. Elevated extracellular phosphate upregulates VSMC expression of Runx2/Chaf1, the prototypic osteo/chondrogenic transcription factor. Moreover, hyperphosphatemia, a common metabolic insult in patients with CKD, enhances production of apoptotic bodies and matrix vesicles that nucleate vascular mineral deposition. Intriguingly, apoptotic bodies simultaneously upregulate the expression of SDF-1α/CXCL12, because SDF-1α mediates vascular homing of Scal1+ progenitors, medial VSMC vesiculation could help recruit adventitial osteoprogenitors. Whether Scal1+ aortic adventitial cells differentially express Msx2, elaborate canonical Wnts, or contribute to the CVC lineage has yet to be determined. Moreover, the relative contribution of Scal1+ progenitor recruitment versus VSMC “trans-differentiation” to the birth of vascular osteogenic cells has yet to be examined in diabetic MAC and may change if CKD ensues.

What signals recruit vascular BMP2 signaling in diabetes? High glucose concentrations upregulate BMP2 production in pericytes and mesangial myofibroblasts. In response to tumor necrosis factor-α (TNF-α), peroxides, and shear stress, the endothelial cell also produces BMP2 and BMP4. Adipose tissue itself is an endocrine gland that produces TNF-α, interleukin-6, and adipokines. The inflammatory fibrofatty adipose tissue expansion in the periaortic adventitia and aortic valve interstitium before vascular calcification is likely to play an important role in disease initiation (Figure 1). The oxidative stress, inflammation, fatty connective tissue expansion, and neovascularization of the diabetic adventitia can all serve to stimulate aortic production of BMPs, which exert paracrine influence on regional mesenchymal progenitors (Figure 1).

Why don’t all vascular beds calcify in response to metabolic insult and BMP signaling? The answer lies in the number of defense mechanisms that prevent tissue mineralization. Inorganic pyrophosphate (PPi), matrix Gla protein (MGP), and fetuin are chief among these. PPI is a VSMC-generated organic anion that inhibits mineralization and is a physiological substrate that matrix vesicle-associated ALP must hydrolyze to promote calcium deposition. Extracellular PPi is generated by 2 mechanisms. First, the membrane transporter ank directs secretion of PPI. Second, the enzyme ectonucleotide pyrophosphatase/phosphodiesterase I (NPP1) cleaves extracellular NTPs to generate PPI. Loss of extracellular PPI from either NPP1 or ank deficiency predisposes to massive aortic calcification. PPI is required to stabilize the VSMC phenotype; VSMCs that cannot generate a PPI-replete extracellular milieu undergo osteo/chondrogenic transdifferentiation. MGP is a calcium-binding matrix protein that binds and inhibits BMP2 induction of ALP. In addition, carboxylated MGP produced by VSMCs binds matrix elastin and inhibits calcification. Mice lacking MGP develop profound panarterial vascular calcification (endochondral ossification) and die from aortic rupture. The diverse roles of BMP2 and BMP4 during vasculogenesis and development are regulated by a diverse cadre of vascular BMP inhibitors. Intracellular defenses to osteogenic vascular BMP signaling also exist; Smad6, an inhibitory vascular Smad, attenuates BMP2 activation of receptor Smad trans-activators. Mice lacking Smad6 develop aortic valve and outflow tract ossification. Fetuin is an important humoral inhibitor of soft tissue mineralization that controls the metabolism of vascular matrix vesicles (vide infra). Deficiencies in serum fetuin arising from genetic, inflammatory, or metabolic insult promote widespread tissue calcium deposition (eg, heart and lung) that curiously spares the aorta in mouse models. Other molecules such as osteopontin have more complex roles, inhibiting calcification but also promoting calcium egress via extracellular matrix acidification. Procalcific vascular cytokine signaling is held in check by osteoprotegerin, most probably via inhibition of RANKL.

Thus, in addition to the upregulation of pro-osteogenic signals, inhibitors of mineral accumulation must be inactivated to permit robust aortic calcification. Both regulatory arms are profoundly perturbed in CKD. The mechanisms controlling aortic MAC in CKD overlap those of diabetes; however, the hyperphosphatemia, reduced serum Pi and fetuin, and secondary hyperparathyroidism of CKD accentuate aortic calcium accumulation. Hyperphosphatemia promotes VSMC matrix vesicle formation. Intriguingly, matrix vesicles may either promote or inhibit calcium deposition, dependent on whether fetuin is recruited. Moreover, fetuin promotes “phagocytotic clearance” of pro-osteogenic matrix vesicles. Thus, in the setting of CKD, reduced serum fetuin levels contribute to the vascular procalcific milieu.

Electron microscopy studies of human postmortem specimens demonstrated early on that aortic calcium deposition in both MAC and atherosclerosis initiates at lipid vesicles located along and between elastic laminae but not within the elastin fibers. However, aortic calcification in association with primary alterations in elastin matrix metabolism represents a unique entry point in a feed-forward cycle of MAC. The most aggressive drug-induced animal models of MAC combine either nicotine, a stimulus for elastinolysis, or warfarin, a mechanism for inhibiting MGP–elastin interaction, with excessive vitamin D. Ex vivo, devitalized aortic valves and aortas depleted of VSMCs and myofibro-
blasts, the sources of matrix vesicles, can calcify by elastin-mediated nucleation.\textsuperscript{55-57} However, matrix-bound lipids still play a role because ethanolic delipidation inhibits ex vivo calcium deposition of devitalized aortic valves.\textsuperscript{55} In vivo, aberrant elastin organization and metabolism is characterized by aortic root dilatation and MAC, as evident in Marfan syndrome. Primary fibrillin 1 insufficiency causes abnormal adventitial microfibrillar matrix organization,\textsuperscript{58} secondary changes in elastin metabolism impair medial VSMC terminal differentiation\textsuperscript{59} and promote elastin-nucleated medial calcification.\textsuperscript{58} Direct elastin-nucleated calcification also occurs in pseudoxanthoma elasticum,\textsuperscript{60} electron microscopy confirms calcium deposition along elastin fibers in the absence of matrix vesicle formation.\textsuperscript{60} Thus, although mechanisms are still being elucidated, altered elastin matrix metabolism enhances aortic calcium deposition and VSMC phenotypic drift.\textsuperscript{58,59} Because calcium phosphate mineral deposition suppresses VSMC production of tropoelastin,\textsuperscript{61} elastin matrix metabolism no doubt contributes to the progression of vascular calcium load in all forms of MAC.

**Atherosclerotic Aortic Calcification**

Mechanisms of aortic atherosclerotic calcification are overlapping yet distinct from those of MAC. This form of aortic calcium deposition, the type Vb atherosclerotic plaque,\textsuperscript{62} has been described excellently\textsuperscript{1} and will be considered only briefly. Atherosclerotic calcification is intimately oriented, eccentric, initiating at the base of necrotic fibrofatty plaques via apoptotic vesicles arising from dead and dying VSMCs.\textsuperscript{1,62} Adjacent chondrogenic and osteogenic processes are recruited by CVC activation and contribute to procalcific matrix remodeling.\textsuperscript{63} As in endochondral bone formation, ALP induction, Cbfal/Runx2 and Msx2 expression, type II and type I collagen deposition, and angiogenic invasion are salient components.\textsuperscript{63} The initiating stimuli are inflammatory and redox dependent,\textsuperscript{64} and bone morphogens are recruited with disease progression.\textsuperscript{64} Indeed, Demer first identified vascular BMP2 expression within calcifying atherosclerotic plaques.\textsuperscript{6} Oxidation of cholesterol-laden lipoprotein deposits generate bioactive oxysterols that synergize with vascular BMP2 to promote ectopic osteogenic gene regulatory programs.\textsuperscript{55}

Major features of atherosclerotic calcification that differ from diabetic MAC include abundant fibrosis, extensive cellular necrosis, apoptotic body formation, and cholesterol crystal accumulation that can support some epixial calcium phosphate deposition.\textsuperscript{1,14,50,66} By histology, endochondral bone formation very commonly ensues; in advanced disease, this ectopic bone can support hematopoietic marrow elements.\textsuperscript{6} The high level of Cbfal/Runx2 observed in calcifying atherosclerotic plaques is particularly important.\textsuperscript{38,48,63} In addition to promoting ALP expression, Runx2: (1) strongly promotes expression of type I collagen, and (2) upregulates the expression of vascular endothelial growth factor, the prototypic osteogenic–angiogenic coupling factor.\textsuperscript{67} Karsenty demonstrated that sustained ectopic expression of dermal ALP with the regional type I collagen deposition was sufficient to drive heterotopic dermal mineralization.\textsuperscript{68} However, this type of ectopic dermal mineralization was not associated with matrix vesicles or apoptotic bodies that characterize MAC or atherosclerotic calcification.\textsuperscript{12-14,17,50} Thus, drawing on lessons learned from skeletal development, synergistic interactions between paracrine BMP and vascular endothelial growth factor signaling with neoangiogenesis, robust aortic expression of Runx2, matrixrine cues provided by type I collagen accumulation, and vascular lipidaceous matrix vesicle production likely combine to drive ectopic bone formation in advanced type Vb plaques.\textsuperscript{1}

**Aortic Valve Calcification**

Approximately 30% of patients ≥65 years of age have echocardiographic evidence of aortic sclerosis, with 2% overall exhibiting aortic stenosis.\textsuperscript{69} Calcium deposition is a particularly ominous feature of aortic valve disease; in patients with asymptomatic aortic stenosis, moderate to severe valve calcification is the single most significant determinant of clinical disease progression.\textsuperscript{70} In a cross-sectional study, Otto described the histopathologic progression of aortic valve calcification.\textsuperscript{71,72} In many ways, the early changes of the aortic valve interstitium\textsuperscript{72} are reminiscent of those described in the tunica adventitia with diabetes and dyslipidemia (vide supra). Similar inflammatory histology occurs in calcifying bicuspid aortic valves in the complete absence of atherosclerosis.\textsuperscript{73}

Thus, aortic valve calcification occurs in response to mechanical stressors, inflammation, and the metabolic challenges of diabetes, dyslipidemia, and uremia.\textsuperscript{1,38,74,75} During disease progression, histological and molecular analyses clearly demonstrate that a phase of active osteogenic mineral deposition contributes to vascular calcium accumulation. By histology, this appears to occur principally via nonendochondral processes in aortic valves,\textsuperscript{75} although the chondrogenic transcription factor Sox9 is upregulated in both calcifying and noncalcifying diseased valves.\textsuperscript{76} In advanced disease, woven bone formation is histologically evident in 13% of cases.\textsuperscript{77} At the molecular level, active BMP–Msx2-Wnt signaling is detectable in virtually all calcifying aortic valves\textsuperscript{76,77} (D.A. Towler, unpublished data). However, by histology, massive concretions of acellular amorphous calcium phosphate are also seen, suggesting that profound epixial mineral deposition occurs once cell-based mineralization has initiated.\textsuperscript{77} The disappointing effects of statins on the progression of established aortic valve calcification may reflect this fact.\textsuperscript{78}

Mechanisms controlling initiation and progression of aortic valve calcification are poorly understood, largely because of the limitations of current animal models. Rajamannan first demonstrated that aortic myofibroblasts undergo osteogenic trans-differentiation.\textsuperscript{76,79} Pharmacological doses of statins prevented osteogenic trans-differentiation of aortic valve myofibroblasts in culture.\textsuperscript{79} Recently, she has identified the mechanistic underpinnings; Wnt/LRP5/\beta-catenin signaling, a signaling cascade absolutely required for osteoblast differentiation in the skeleton,\textsuperscript{80} is activated by oxidized LDL.
cholesterol in valve myofibroblasts and is inhibited by statin administration. This elegant work provides robust evidence that mineral deposition directed by aortic valve myofibroblasts is osteogenic in nature and is potentially preventable via pharmacological intervention.

Summary

Over the past 25 years, we have learned much concerning the biology of aortic calcification. Active mineralization mechanisms clearly resembling those of skeletal endochondral and membranous ossification participate in vascular calcium accumulation. However, the endocrine physiology of vascular calcium deposition and its turnover is poorly understood and will depend on the histoanatomic, mechanical, developmental, matricrine, and metabolic features of the diseased vascular segment. Many fundamental questions remain to be addressed. The field of vascular matrix vesicle metabolism is in its infancy; mechanisms whereby cells shed and endocytose vascular matrix vesicles and how osteogenic morphogens and matrix control these processes are poorly characterized. The origins of vascular osteoprogenitors must be clearly delineated. Although circulating progenitors may contribute, most mineralizing osteoprogenitors appear locally recruited in response to paracrine osteogenic cues or hyperphosphatemic stimulation. The “paracrinology” of vascular adventitial–medial signaling and its metabolic regulation is poorly characterized. Although canonical Wnt signals are capable of mediating these interactions, the specific LRP5 and LRP6 ligands that participate in vascular Wnt signaling cascades have yet to be determined.

Novel therapeutics are needed. Dependent on disease stage and setting, the metabolic, endocrine, inflammatory, elastinolytic, and mechanical insults will differ in relative contribution to the extent of aortic calcification. Stage-specific mechanisms contributing to calcific aortic disease must be carefully considered as clinical studies are designed and therapeutic strategies crafted. Given the benefits of sevelamer on aortic calcification in dialysis patients, this phosphate- and sterol-binding resin also holds promise for diabetic patients with declining renal function. Although statins cannot treat established aortic valve calcification, early treatment with statins may prevent valve mineralization, particularly in high-risk patients after bioprosthetic valve implantation. Small studies suggest that bisphosphonates can inhibit aortic mineral deposition in extant disease; the absence of a robust murine model of calcific aortic stenosis remains a major scientific shortcoming. This limits our ability to examine how strategies targeting inflammation, oxidative stress, morphogen signaling, angiogenesis, matrix metabolism, and epitelial mineral deposition may differentially influence initiation versus progression phases of aortic stenosis. Nevertheless, given the blossoming field of cardiovascular endocrinology, the near future holds tremendous promise that new pharmacotherapies will emerge to help address the unmet clinical need in calcific aortic disease.

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