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Coronary arterial calcification: A review of mechanisms, promoters and imaging☆

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ABSTRACT

Coronary artery calcification (CAC) was once thought to be a passive, degenerative, and quiescent development of disease. However, it has now been shown to be an active process associated with atherosclerosis that is stimulated by inflammatory pathways. Calcification forms within the intimal and medial layers of the vessel wall by way of mechanisms similar to bone development. A variety of imaging modalities have been used to identify and characterize CAC, from early microcalcifications to well-developed fibroatheromas that have calcified. There are sex and race differences in prevalence and development of CAC, and medical therapies such as statin and warfarin use exhibit pro-calcific effects on the vessel wall. Effective medical treatment of CAC has yet to be established; therefore a greater understanding of the factors that induce calcification is needed to develop appropriate therapeutic strategies.

Introduction

Coronary artery calcification (CAC), characterized by the pathological deposition of mineral in the artery wall, is recognized to be associated with atherosclerosis. The development of CAC has been traditionally considered as a passive, degenerative, and quiescent development of disease, as a result of mechanisms similar to bone development [1]. Prior observations supported the concept that the prevalence of calcification is greater in patients with stable forms of coronary artery disease (CAD) [2,3], and is more resistant to modification with anti-atherosclerotic medical therapies [4]. Yet, evidence now supports the concept that the development of *de novo* CAC is an active process, stimulated by inflammatory pathways, characteristic of the systemic inflammation of metabolic syndrome and type 2 diabetes [5]. In the early stages of CAC development, inflammatory cytokines have been shown to activate osteogenic differentiation and mineralization of vascular cells. Advanced calcification associates with increased mineralization and a decrease in macrophage content [6]. Imaging and clinical studies demonstrate calcium to play differential roles throughout the life course of atherosclerotic plaque. As such, depending upon the specific scenario (i.e. natural plaque progression associated with *de novo* spotty calcification vs. statin-induced plaque regression and subsequent plaque calcification as examples), coronary calcification *per se* may underscore a variety of pathophysiological states that range from promoting plaque vulnerability, to the converse, where it may be the consequence of plaque delipidation and stabilization in response to anti-atherosclerotic therapies. Hence the clinical implications of coronary calcification remain highly variable.

Candidate mechanisms

The mechanisms promoting *de novo* vascular calcification fall into two broad categories (Fig. 1). The first being loss of inhibitors of mineralization such as osteopontin, fetuin, and γ-carboxyglutamic acid Gla protein. The second, induction of osteogenesis, is a consequence of active bone formation *in situ* by osteoblast-type cells. Various hypotheses have described the origin of these cells, such as vascular smooth muscle cells (VSMCs), which may be induced toward the osteoblastic phenotype [5,7]. Matrix vesicles that regulate mineralization are produced in the intima and media of VSMCs [8]. These cells also have been shown to undergo differentiation when stimulated by oxidative stress, bone

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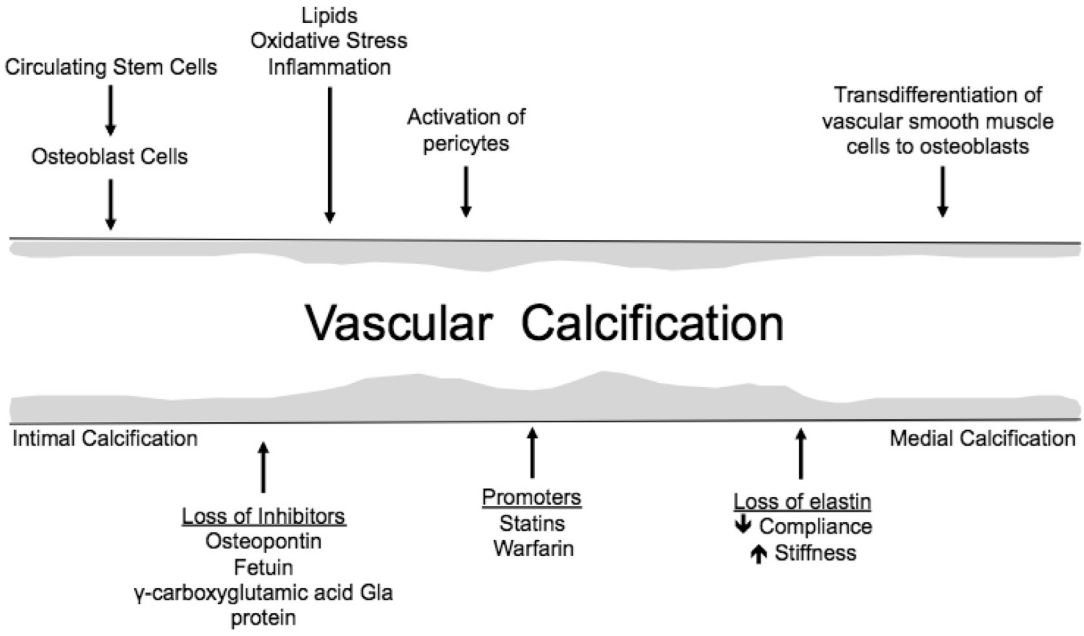

Fig. 1. Mechanisms and mediators of vascular calcification.

morphogenetic proteins, or changes in pyrophosphate levels. The signaling pathway, Bmp-Msx2-Wnt, is then induced to regulate the pathogenesis of vascular calcification [9–11]. Activation of nascent resident pericytes or circulating stem cells may lead to an osteochondrogenic phenotype. When placed in an atherosclerotic environment, these cells have exhibited responses to factors such as oxidized LDL (low density lipoprotein) by becoming destabilized to form nodules, similar to bone formation, and subsequently calcify [12]. The balance between promotion and inhibition of calcification becomes dysregulated in diabetes, chronic kidney disease, and atherosclerosis, in the second mechanism of vascular calcification [13].

Vascular calcification occurs within the intimal and medial layers of the vessel wall. Calcification of the media, also known as Mönckeberg sclerosis, is found within the muscular layer of the artery composed of smooth muscle cells and elastin rich extracellular matrix. Medial calcification occurs preferentially along the elastic lamina, and the non-occlusive process of mineralization of the elastic fibers appears to be directly pathogenic by decreasing vascular compliance. The associated rise in high blood pressure is a result of the stiffening of the vessel wall. Medial calcification has been shown to be associated with hypertension, diabetes, chronic kidney disease, and osteoporosis [14].

Conversely, intimal calcification forms at the site of an atherosclerotic lesion. The intimal layer of a normal vessel is composed of endothelial cells along with a small amount of subendothelial connective tissue. The intima thickens and becomes considerably inflamed where cholesterol is deposited, and cellular necrosis occurs. As atherosclerosis progresses, calcium develops within these lesions. Calcification of coronary arteries has been directly correlated with atheroma volume in a large pathological study of human coronary arteries [15]. However, recent studies have suggested that not all vascular calcification indicates an equivalent atherosclerotic risk, as the distribution and morphology of atheroma calcium should be considered. Heavily calcified plaques may be more stable, and plaques more vulnerable to rupture may be mixed lesions of calcified and uncalcified tissue [16]. While our understanding of the molecular mechanisms of calcium have improved in recent decades, further mechanistic insights are required that lead to therapeutic strategies that inhibit *de novo* vascular calcification to promote plaque stability.

Biomarkers of calcification

A number of markers of calcification have been identified. Fetuin-A, a liver-derived plasma protein, has a high affinity for bone mineral [17]. This protein also has the ability to prevent the precipitation of basic calcium phosphates from supersaturated solutions, suggestive of its potent systemic inhibition properties of soft tissue calcification [18–21]. Animal data have shown that fetuin-A-deficient mice develop extensive soft tissue calcifications in the myocardium, kidney, tongue, and skin [22,23]. In the clinical setting, hemodialysis patients with lower serum fetuin were associated with an increase in mortality [22]. Matrix Gla protein (MGP), a vitamin K–dependent protein, plays a role in preventing soft tissue calcification and local mineralization of the vascular wall by inhibiting bone morphogenetic protein BMP/ BMPR2 interactions as well as by binding BMP2 directly [24,25]. In animal models, MGP-null mice develop extensive and lethal medial calcification [26]. The severity of CAC, as measured by EBCT, increased as serum MGP levels decreased in a study of 115 subjects with suspected coronary artery disease [27]. Alkaline phosphatase (ALP), an enzyme that catalyzes the hydrolysis of organic pyrophosphate [28], an inhibitor of vascular calcification [29], is predominately expressed in liver, kidney, and bone [28]. ALP is expressed at high levels in medial SMCs in the presence of medial calcification. While atherosclerotic vascular calcification stimuli, such as oxidized LDL, also has shown increased ALP activity in cultured VSMCs [30].

Assessing plaque calcium—invasive imaging modalities

The wealth of epidemiological data concerning arterial calcification stems from single time-point imaging data of human coronary arteries using computed tomography (CT). However, invasive coronary imaging modalities harboring greater image resolution to evaluate morphology have shed further light onto the mechanistic implications of plaque calcification and their respective