JACC: CARDIOVASCULAR IMAGING
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PUBLISHED BY ELSEVIER

VOL. 11, NO. 1, 2018
ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2017.10.012

REVIEW

STATE-OF-THE-ART PAPER

Coronary Artery Calcification and its Progression

What Does it Really Mean?

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ABSTRACT

Coronary artery calcification is concomitant with the development of advanced atherosclerosis. Coronary artery calcification pathologically begins as microcalcifications (0.5 to 15.0 μm) and grows into larger calcium fragments, which eventually result in sheet-like deposits (>3 mm). This evolution is observed to occur concurrently with the progression of plaque. These fragments and sheets of calcification can be easily identified by radiography as well as by computed tomography and intravascular imaging. Many imaging modalities have proposed spotty calcification to be a predictor of unstable plaque and have suggested more extensive calcification to be associated with stable plaques and perhaps the use of statin therapy. We will review the pathology of coronary calcification in humans with a focus on risk factors, relationship with plaque progression, correlation with plaque (in)stability, and effect of pharmacologic interventions. (J Am Coll Cardiol Img 2018;11:127–42) © 2018 by the American College of Cardiology Foundation.

The presence of calcification has been recognized in atherosclerotic coronary arteries for more than a century. Coronary artery calcification (CAC) implies the presence of coronary artery disease (CAD) irrespective of risk factors or symptoms, is concomitant with the development of advanced atherosclerosis (1), and is an established predictor of future cardiac events (2,3). Generally, CAC correlates with the extent of CAD. The presence and extent of CAC can be assessed by various imaging modalities with computed tomography (CT) having the most available correlation with prognostic outcomes data. Both the extent of calcification as well as its pattern has prognostic implications. In general, spotty calcification is more commonly associated with unstable plaques and extensive calcification more so with stable plaques, but the relationship of CAC to plaque instability is extremely complex and incompletely understood. In this review, we will focus on human CAC from a pathologic standpoint and explore its implications with regards to plaque progression and the relationship of the extent and patterns of calcification to plaque morphology as seen pathologically and radiographically. We will also explore the effects of various principle risk factors and pharmacologic interventions on CAC. Pathophysiological

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Manuscript received August 10, 2017; revised manuscript received September 29, 2017, accepted October 12, 2017.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

AMI = acute myocardial infarction

BMP = bone morphogenetic protein

CAC = coronary artery calcification

CHD = coronary heart disease

CT = computed tomography

HU = Hounsfield unit

IVUS = intravascular ultrasonography

OCT = optical coherence tomography

OFDI = optical frequency domain imaging

TCFA = thin-cap fibroatheroma

mechanisms of calcification, as understood from correlating pathology and imaging, will be examined to offer a pathological perspective for predicting risk of future events.

TYPES AND PATHOLOGY OF CALCIFICATION IN ATHEROSCLEROSIS

Vascular calcification can be classified into 2 distinct forms depending on its location within the intima (intimal calcification) or in the vascular medial layer. Medial calcification mostly affects the peripheral arteries of the lower extremities, resulting in the loss of elasticity, and is routinely observed in patients with peripheral vascular disease. Furthermore, the progression of arterial medial calcification is reported to be associated with renal failure, hypercalcemia, hyperphosphatemia, parathyroid hormone abnormalities, and duration of dialysis. Meanwhile, intimal calcification is the dominant type of calcification seen in coronary arteries. Therefore, we will mainly focus our discussion on intimal calcification in this article.

The earliest form of CAC is microcalcification seen in lesions with pathological intimal thickening with a size ranging from 0.5 to 15.0 μm (4–6), observed best by special stains for calcium such as von Kossa and Alizarine red (**Figure 1A**). Within the lipid pool, early microcalcification is visible by light microscopy and is thought to originate from smooth muscle cell (SMC) apoptosis (4,6,7). Initial calcification occurring in matrix vesicles with a diameter from 100 to 700 nm can only be observed by electron microscopic examination (8). In addition to SMC apoptosis, macrophage-derived matrix vesicles also play a role in the process of microcalcification (9). SMC apoptosis leads to fine microcalcifications, whereas apoptotic macrophages produce relatively larger punctate appearance (**Figures 1B and 1C**). These calcific deposits are commonly seen in the deeper areas of necrotic core close to internal elastic lamina (**Figure 1D and 1E**). Microcalcifications coalesce into larger masses over time to form speckles and fragments of calcifications. The progression of calcification occurs from the outer rim of the necrotic core into the surrounding collagenous matrix (**Figure 1F**); the central core may or may not become calcified at this stage. Further progression of calcification leads to calcified plaques typically with calcified sheets or plates (>1 quadrant), involving SMCs and collagenous matrix regardless of the necrotic core (**Figure 1G and 1H**). Calcified sheets may fracture leading to the formation of nodular calcification (**Figure 1I**). These nodules may extend into the lumen or the media and can be associated with fibrin deposition. These protuberant nodules can lead to discontinuity of the endothelial lining and underlying collagen matrix, and acute luminal thrombosis. The calcified nodule is the underlying mechanism of acute coronary events in 2% to 7% of coronary artery thrombosis (10) and 4% to 14% of the carotid artery thrombosis (11) in pathological studies.

Bone formation (12) comprising trabecula with marrow space is rarely seen in CAD within calcific regions (**Figure 1J**). When observed, it is usually seen in heavily calcified segments of the arterial wall suggesting that osteogenesis might be exclusively associated with severe arterial calcification. In amputated lower limbs due to peripheral artery disease, the incidence of bone formation has been reported to be as high as 19% (13). It has been suggested that the process of arterial calcification shares some features with skeletal bone formation, including chondrocyte and osteoblast differentiation, mineralization, and bone matrix deposition and resorption. Bone-related proteins such as bone morphogenetic protein (BMP)-1 and BMP-4, bone sialoprotein, osteocalcin, osteonectin, osteopontin, and osteoprotegerin have been identified in calcified arteries (14,15). In early coronary plaques, osteoprotegerin, osteopontin, and matrix Gla protein have been reported at sites of microcalcification; uncarboxylated matrix Gla protein expression is not seen in adaptive intimal thickening (AIT) but evolves with the development of pathologic intimal thickening (PIT) and fibroatheromas (15). BMP-2, BMP-4, osteopontin, and osteonectin are more prevalent in lesions with bone formation in fibrocalcific plaques. Although bone-related protein expression exists from early stages of plaque formation, the precise mechanisms of calcification or osteogenesis in atherosclerosis have remained uncertain.

There are various stimuli in the initiation and progression of calcification which may differ depending upon the stage of plaque as well as the surrounding milieu. As alluded to above, we believe that the death of SMCs is the driving force for early microcalcification (1). This is followed by infiltration of macrophages into the lipid pool which also undergoes cell death and calcification. Cell death provides phospholipid-rich debris that serves to nucleate apatite, a process that starts within lipid pools and progresses with inflammation and further cell death, leading to the development of a necrotic core.