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Atherosclerosis newsletter

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The two issues of *Atherosclerosis* published in August contain several review articles and the accompanying commentary by Drs. Fadini and Rattazzi on "Calcification, from basic mechanisms to clinical implications" as well as two original articles on the same topic.

Innate and adaptive immunity in cardiovascular calcification

The prevalence of vascular and valvular calcification is increasing and remains a leading contributor of cardiovascular morbidity and mortality. Studies have provided accumulating evidence that cardiovascular calcification is an inflammatory disease in which innate immune signaling becomes sustained and/or excessive, shaping a deleterious adaptive response. The triggering immune factors and subsequent inflammatory events surrounding cardiovascular calcification remain poorly understood, despite sustained significant research interest and support in the field. Most studies on cardiovascular calcification focus on innate cells, particularly macrophages' ability to release pro-osteogenic cytokines and calcification-prone extracellular vesicles and apoptotic bodies. Even though substantial evidence demonstrates that macrophages are key components in triggering cardiovascular calcification, the crosstalk between innate and adaptive immune cell components has not been adequately addressed. The only therapeutic options currently used are invasive procedures by surgery or transcatheter intervention. However, no approved drug has shown prophylactic or therapeutic effectiveness. Conventional diagnostic imaging is currently the best method for detecting, measuring, and assisting in the treatment of calcification. However, these common imaging modalities are unable to detect early subclinical stages of disease at the level of microcalcifications; therefore, the vast majority of patients are diagnosed when macrocalcifications are already established. In this review, Passos et al. unravel the current knowledge of how innate and adaptive immunity regulate cardiovascular calcification; and put forward differences and similarities between vascular and valvular disease.

New insights into endogenous mechanisms of protection against arterial calcification

Cardiovascular complications due to accelerated atherosclerosis and arterial stiffening are the leading cause of morbidity and mortality in the Western society. Both pathologies are frequently associated with vascular calcification. Deposits of calcium phosphate salts is the hallmark of vascular calcification. Calcification is frequently observed in atherosclerotic lesions (intimal calcification) associated with vascular smooth muscle cells (VSMCs) and macrophages. By contrast, medial calcification, occurring in the elastic region of the arteries, is almost exclusively associated with VSMCs, and is common in arteriosclerosis related to aging, diabetes, and chronic kidney disease. In extracellular fluids, a range of endogenous low- and high-molecular weight calcification inhibitors are present, including osteopontin, matrix-Gla proteins and Fetuin A. Moreover, pyrophosphate deficiency plays a key role in vascular calcification. Loss of function in the enzymes and transporters involved in the extracellular pyrophosphate metabolism leads to excessive deposition of calcium-phosphate salts. In this review, Villa-Bellosta summarizes the current knowledge about endogenous mechanisms of protection against calcification in the aortic wall, focusing on the role of extracellular pyrophosphate metabolism in vascular smooth muscle cells and macrophages.

Calcium deposition within coronary atherosclerotic lesion: Implications for plaque stability

In this review, Jinnouchi et al. describe the relationship between calcium deposition and the progression of atherosclerosis.

Atherosclerotic lesion progression is associated with intimal calcification. The earliest lesion that shows calcification is pathologic intimal thickening in which calcifications appear as microcalcifications. The calcifications become larger as plaques progress, becoming punctate, fragmented, and eventually sheet-like calcification. Lesions of acute thrombi show much less calcification than stable fibrocalcific plaques. Conversely, a calcified nodule occurs in highly calcified lesions. Pro-inflammatory cytokines observed in unstable plaques may provoke an early phase of osteogenic differentiation of smooth muscle cells (SMCs), a release of calcifying extracellular matrix vesicles, and/or induce apoptosis of macrophages and SMCs, which also calcify. Recent pathologic and imaging based studies indicate that lesions with dense calcifications are more likely to be stable plaques, while micro, punctate, or fragmented calcifications are associated with either early stage plaques or unstable lesions. Clinical non-invasive computed tomography (CT) studies show that the greater the calcium score, the higher the likelihood of patients developing future acute coronary events. This appears contradictory with the findings from pathologic autopsy studies. However, CT analysis of calcium subtypes is limited by resolution and blooming artifacts. Thus, areas of heavy

calcification may not be the cause of future events as pathologic studies suggest. Rather, calcium may be an overall marker for the extent of disease. These types of discrepancies can perhaps be resolved by invasive or non-invasive high resolution imaging studies carried out at intervals in patients who present with acute coronary syndromes versus stable angina patients. Coronary calcium burden is greater in stable plaques than unstable plaques and there is a negative correlation between necrotic core area and area of calcification. Recent clinical studies have demonstrated that statins can reduce plaque burden by demonstrating a reduction in percent and total atheroma volume. However, calcification volume increases. In summary, pathologic studies show that sheet calcification is highly prevalent in stable plaques, while microcalcifications, punctate, and fragmented calcifications are more frequent in unstable lesions. Both pathologic and detailed analysis of imaging studies in living patients can resolve some of the controversies in our understanding of coronary calcification.

Innovation in medical imaging to improve disease staging, therapeutic intervention, and clinical outcomes

Calcification plays an important role in the pathogenesis of atherosclerosis and begins early on in the disease process. The presence of calcium has long been seen as a surrogate marker of atherosclerosis and is a well-established predictor of cardiac risk. Evidence suggests that different calcification patterns are associated with different histopathological and clinical features. At the patient level, the presence of macrocalcification, as assessed by the coronary calcium score, confers worst outcomes. At the plaque level, microcalcification rather than macrocalcification denotes plaque vulnerability. In this review, Daghem and Newby describe improved non-invasive imaging modalities that may allow for a more comprehensive assessment of atherosclerotic calcification and help identify patients at increased risk of clinical sequelae.

Aortic valve calcification predicts all-cause mortality independent of coronary calcification and severe stenosis

Calcific aortic valve disease (CAVD) is highly prevalent in patients with significant smoking history and is a marker of atherosclerosis. Since smoking is a major risk factor for both CAVD and progressive coronary artery disease (CAD) from atherosclerosis, and current guidelines recommend routine lung cancer screening with low dose CT (LCSCT) in this population, Christensen et al. assessed the prognostic value of reporting aortic valve calcification (AVC) from LCSCT for all-cause mortality, independent of traditional cardiovascular risk factors including CAC, in this moderate-to-high risk cohort.

They performed a single site, retrospective analysis of 1529 moderate-to-high atherosclerotic cardiovascular risk U.S. veterans, who underwent clinically indicated LCSCT. CTs were scored for AVC and coronary artery calcification (CAC). The primary endpoint was all-cause mortality and secondary endpoints were nonfatal myocardial infarction (MI) and nonfatal cerebrovascular accident (CVA).
Over a 4-year follow-up, 227 patients died, 112 had nonfatal MI, and 52 had nonfatal CVA. AVC was predictive of all-cause mortality, and this association remained significant after multivariate adjustment for traditional atherosclerotic risk factors, including CAC. After excluding patients with severe aortic stenosis (AS) or severe AVC, in a subset of 765 patients who had echocardiograms, this association remained significant after multivariate analysis. Despite controlling for CAC in the models, AVC was still associated with MI and CVA.

Scoring AVC derived from LCSCT is predictive of mortality, nonfatal MI, and nonfatal CVA in patients at known risk for cardiovascular disease, independent of coronary calcification or severe aortic valve stenosis.

Progression of valvular calcification and risk of incident stroke: The Multi-Ethnic Study of Atherosclerosis (MESA)

Stroke is a leading cause of long-term disability and the 5th leading cause of death in the United States. Prevalent valvular calcification (VC) is associated with stroke but little is known about associations of VC progression with stroke. Fashanu et al. explored the impact of VC progression on incident total and ischemic stroke risk in a multiethnic cohort using Cox regression adjusted for cardiovascular disease (CVD) risk factors.

They studied 5539 Multi-Ethnic Study of Atherosclerosis (MESA) participants free of baseline CVD and atrial fibrillation. Baseline mean ± SD age was 62 ± 10 years; 53% were female; 83% had no progression of VC; 15% progression at one site (mitral annular calcification (MAC) and aortic valve calcification (AVC)), and 3% progression at both sites. Over a median of 12 years, 211 total and 167 ischemic strokes occurred. The number of sites with VC progression was not associated with total and ischemic stroke. MAC progression was associated with increased risk of total stroke. Results remained significant after further adjustment for baseline coronary artery calcification. After excluding participants with interim atrial fibrillation and coronary heart disease, findings were no longer statistically significant in fully-adjusted models. There was no interaction by age, sex, or race/ethnicity. There was no association with AVC progression and stroke.

These results show that progression of MAC but not AVC is associated with increased risk of total and ischemic stroke.