

The Role of Intimal Arterial Calcification in the Context of Atherosclerotic Plaque Stability

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Cardiovascular diseases are the leading cause of death in the Western countries despite the improvement in the diagnosis and treatment of affected patients [1]. Atherosclerotic process and its complications are the main determinants of cardiovascular diseases' development. In particular, the development of an inflammatory, systemic condition of the vessels is able to increase the generation of the atherosclerotic plaques and makes them to become unstable and more prone to rupture [1,2]. Although histology and cytology has already explained the inner determinants of the atherosclerotic plaque, the cells implicated in the negative and positive remodeling of the vascular walls and the inflammatory conditions within the plaques, some point still remain obscure [2-4]. In particular, the receptor activator of nuclear factor (NF)κB ligand (RANKL)/receptor activator of nuclear factor (NF)κB (RANK)/osteoprotegerin (OPG) system has emerged as playing a key role in the genesis of atherosclerotic plaque composition and intima arterial calcification [2,3,5].

Intima arterial calcification is a key features of atherosclerotic development within arterial walls [6] and osteoprotegerin and its biochemical pathway is able to promote such a relationship [2]. It is possible that atherosclerotic inflammatory condition is able to promote the release of osteoprotegerin and soluble RANKL from smooth muscle cells and endothelial cells [2]. The consequence of this release process is the imbalance between osteoclast-like cells (such as monocytes/macrophages, dendritic cells, and smooth muscle cells) and their action in mineral re-absorption from vascular walls (all inhibited) and the osteoblast-like cell mineral deposition (increased activity) [2,6,7]. This impairment leads to the arterial intimal calcification often observed within atherosclerotic plaques.

What is the role of this calcification is still under debate [8]. A recent work from Maldonado et al. [9] pointed out novel insights in the role of plaque calcification in the economy of cardiovascular diseases progression. The original hypothesis is that microcalcification in the context of intima can promote the instability of the plaque and the vulnerability of this structure to biomechanical alterations [9]. The authors studied 92 human coronary arteries by means of high-resolution microcomputed tomography at 6.7 μm resolution and undecalcified histology with special emphasis on calcified particles <50 μm in diameter. They found that the presence of microcalcification within the fibrous caps was associated to an increased instability of the plaque. This condition was due to a 2.1-fold-increase in the local stress at the poles of the microcalcifications spot and a 5-fold-increase in the circumferential stress of the vascular wall when microcalcifications were gathered together [9]. The results from Maldonado et al. [9] corroborate those coming from the researches of our group [10]. We analyzed the histological features of 72 carotid endarterectomy specimens and compared these results with patients' clinical events after a 12-months follow-up. The results outlined that the degree of carotid plaque calcifications was enhanced in patients who suffered from acute coronary syndrome or developed it during the follow-up period [10].

Nevertheless, a peculiar analysis came from Mauriello et al. [11]. In their elegant morphologic and morphometric study, these authors

evaluated 960 coronary segments from patients died due to acute myocardial infarction (AMI patients) or non-cardiac conditions (controls). Their findings outlined that effectively the calcification burden was higher in AMI patients than controls, as well as calcification area of the plaques. Nevertheless, the calcification degree of the plaques was not related to their instability. The authors supposed that intima arterial calcification was able to identify vulnerable patients, i.e. individuals who are at risk for cardiovascular events, although this does not mean that such persons have unstable plaques [11].

These results outlined the need of further studies able to make more clear the question whether intimal arterial calcification is a real picture of plaque instability or rather a pure marker for the identification of a vulnerable patient.

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