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Review

Vascular calcification in rheumatoid arthritis: Prevalence, pathophysiological aspects and potential targets

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ABSTRACT

Individuals with rheumatoid arthritis (RA) are at increased risk for morbidity and mortality from cardiovascular disease. Excess cardiovascular mortality in RA patients cannot be fully explained by conventional cardiovascular risk factors. The purpose of this review is to discuss recent progress concerning the prevalence and pathophysiological aspects of vascular calcification in RA. RA patients have early-onset diffuse calcification involving multiple vascular beds compared to age and sex-matched controls. Pathogenesis of vascular calcification in RA patients is not fully understood, but specific mediators such as proinflammatory cytokines and not global inflammation could be involved. The possible link between osteoporosis and vascular calcification in RA will not be discussed. Finally, potential targets to reduce vascular calcification in RA will be discussed.

Contents

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1. Rheumatoid arthritis patients present excess cardiovascular mortality

It has been clearly established that the excess mortality associated with rheumatoid arthritis (RA) is mainly due to cardiovascular disease, especially coronary heart disease [1–5]. A meta-analysis was recently conducted to evaluate the incidence of fatal myocardial infarction and stroke events in RA patients [6]. The incidence of fatal myocardial infarction was 13.3 per 1000 RA patient-years (CI: 13–13.6) and the incidence of fatal stroke was 4.5 per 1000 RA patient-years (CI: 4.3–4.7). The relative risk of fatal myocardial infarction in RA patients was about 1.63 compared to the general population (OR = 1.63, CI: 1.34–2). No excess risk was observed for fatal stroke in RA patients [6]. Furthermore, the increased risk for cardiovascular disease cannot be fully explained by conventional cardiovascular risk factors [1,2]. Conventional cardiovascular risk stratification tools, such as the Framingham risk score [7], widely used in primary prevention in the general population, may be less suitable in patients with RA.

Another tool to improve cardiovascular risk stratification is coronary artery calcium (CAC) scoring by computed tomography [8]. High CAC scores have also been associated with increased all-cause mortality, cardiovascular mortality and coronary events [9]. Moreover patients with RA have a higher prevalence and a greater burden of coronary calcification than non-RA controls [10,11].

It may be useful to identify RA patients at high risk for coronary artery disease in order to adopt a more aggressive risk-reducing strategy. However, the clinical value of the CAC risk score as a risk stratification tool has not been clearly validated in the general population and in RA patients. It is noteworthy that coronary heart disease can occur in the absence of coronary artery calcification [12], particularly at the beginning of RA disease [13]. However, vascular calcification used in most studies as subclinical marker of atherosclerosis also constitute an important risk factor for mortality in chronic kidney disease (CKD) and diabetes mellitus patients and many studies have indicated that the risk for cardiovascular events is increased in the presence of vascular calcification [14,15].

Excess cardiovascular mortality in RA patients cannot be fully explained by conventional cardiovascular risk factors. Evaluating coronary artery calcification in RA could help to identify patients at high risk for coronary artery disease, indicating the need for a more aggressive risk-reducing strategy.

2. Types of vascular calcification

Ectopic mineral deposition occurs in many pathologic conditions, including vascular calcification characterized by convergence of bone biology with chronic vascular inflammation. There are conflicting theories about the mechanisms underlying vascular calcification but two main types of vascular calcification are described: atherosclerotic calcification and medial artery calcification [16]. These different types are the consequence of distinct yet overlapping pathological mechanisms, and they are by no means mutually exclusive of one another. Medial and atherosclerotic calcification occur frequently in concert and contribute synergistically to disease [17]. Atherosclerotic calcification occurs at sites of atherosclerotic plaques, where there is a combination of cellular necrosis, inflammation, and cholesterol deposition. Atherosclerotic calcification forms via a process similar to endochondral ossification; chondrogenesis precedes osteoblast induction and lamellar bone formation. As the lesion progresses, osteogenesis is evident [18]. Several studies support the idea that calcium deposition in atherosclerotic plaque is an active and regulated process [19]. In contrast, medial artery calcification proceeds through a process similar to matrix vesicle–mediated intramembranous bone formation, with no cartilage intermediate required [20]. This condition is common in diabetes, chronic kidney disease, aging and probably in rheumatoid arthritis [21]. These features distinguish atherosclerotic calcification and medial artery calcification (organized as bone-like regions) from the dystrophic calcium deposition also frequently observed in vessels in conditions involving chronic inflammation and necrosis.

As we have seen before, the prognostic importance of vascular calcification is also a matter of debate [17]. In atherosclerotic plaque (more than 90% of atherosclerosis fatty plaques undergo calcification), the contribution of focal calcification to plaque vulnerability remains unclear but atherosclerotic plaque calcification is currently used as subclinical marker of atherosclerosis. Medial artery calcification contributes to vascular stiffness and is strongly correlated with coronary artery disease and future cardiovascular events in patients with CKD and in diabetic subjects [14,15]. One of the most important limitations CAC scoring by current techniques, such as electron beam computed tomography, is the difficulty to distinguish between superficial, focal atherosclerotic calcification and deep, concentric medial calcification [17].

3. Genetic disorders associated with vascular calcifications and atherosclerosis

Genetic factors clearly contribute to variation in amounts of media and intimal arterial calcification. Genome-Wide Association Studies (GWAS) have substantially increased our knowledge on risk stratification in CAC and atherosclerosis [22]. Major insight has been provided through rare monogenic human disorders associated with spontaneous, premature artery media calcification: mutations in *ABCC6* in pseudoxanthoma elasticum (PXE), mutations in *ENPP1* in generalized arterial calcification of infancy (GACI) and, most recently, mutations in *NT5E* in another rare disease phenotype consisting of peripheral artery calcification with distal joint calcification caused by CD73 deficiency [23–25]. The underlying disease genes appear to prevent spontaneous calcification within an arterial molecular pathophysiology network modulated by ATP metabolism, inorganic pyrophosphate (PPi), adenosine, and inorganic phosphate (Pi) generation [22]. Since methotrexate increases extracellular adenosine, it would be worthwhile to evaluate its role in the genesis of vascular calcification in future studies in RA patients [26]. No relation of these monogenetic human disorders has been studied in RA but it is known that not all RA patients have the same cardiovascular outcome, and it has been speculated that genetic susceptibility to atherosclerosis may play a role. The HLA-DRB1*0404 is a predisposition gene for RA and it has been associated with the severity of RA. However, RA patients with HLA-DRB1*0404 gene shared epitope-positive have more endothelial dysfunction and particularly increased cardiovascular mortality compared to the epitope-negative RA patients [27,28].