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Editorial

Carotid Intima-Media Thickness in Rheumatoid Arthritis: How Helpful it is to Know the Presence of Subclinical Atherosclerosis?

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Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease associated with a significantly increased risk of cardiovascular mortality mainly due to increased atherosclerotic disease [1-3]. The risk of death is twofold higher in RA patients than in general population and the main cause of mortality is cardiovascular disease (CVD), accounting for about a half of premature deaths observed. The global mortality incidence in RA patients attributable to CVD is approximately 40% [4,5]. Atherosclerosis and RA share genetic and environmental risk factors, as well as, different types of cells and cytokines implicated in their pathogenesis. These factors are well-known to be involved in the development and progression of an inflammatory condition. These facts strongly suggest that patients who develop RA may also be predisposed to develop cardiovascular disease. Indeed, pathophysiology of atherosclerosis in several aspects originates from inflamed synovium in patients with RA, mainly through the infiltration of abnormally activated immune cells, namely, monocytes, macrophages and T helper 1 cells. Serum inflammatory mediators including tumor necrosis factor-a, interleukin 6 and, matrix metalloproteinases play a key role in this inflammatory process [6]. The prevalence of some traditional cardiovascular risk factors is increased in RA. However, since adjustment for these cardiovascular factors does not fully account for the heightened risk, RA itself as inflammatory disease is an independent risk factor for CVD [5,7].

The ultrasound measurement of carotid intima-media thickness (IMT) is a simple, valid, reproducible and standardized noninvasive technique to visualize atherosclerotic burden directly in the arterial wall. There is clear literature evidence that an increased carotid IMT can be regarded as an attractive biomarker of atherosclerosis and of increased cardiovascular risk, potentially useful as a therapeutic target with pharmacological drug agents in those at increased cardiovascular risk. Carotid IMT was found to be higher in RA patients with recent disease onset disease compared with age-matched and sex-matched control individuals [8]. The noninvasive measurement of carotid IMT is thought to reflect structural vessel changes at subclinical stages of atherosclerosis. It is a strong predictor for future vascular events in the general population, especially in those with low-grade inflammation as assessed by C-reactive protein levels [9]. In RA patients with long disease duration over 20 years, the carotid IMT was wider than that in patients of the same age but with shorter disease duration [10]. However, an increased carotid IMT was found to be already present in RA patients as early as within 12 months of symptom onset [8]. These findings clearly support the concept that the high-grade inflammation associated with RA causing joint disease, also accelerates the process of atherosclerosis in these patients. Indeed, inflammation is already present way before signs and symptoms of Atherosclerosis or RA, since persons who do develop RA have elevated C-reactive protein levels many years before the diagnosis of RA [11].

Since systemic inflammation and continuously high disease activity in RA patients contribute to excessive prevalence of CVD, it is interesting to know what happens in RA patients with low disease activity. In this regard, Biskup M., *et al.* [12] studied last year 70 RA patients without known CVD and 33 healthy controls, of a comparable age. All RA patients had continued low disease activity (DAS28 ≤ 3.2) from

2 to 7 years. The groups were assessed for: blood pressure, serum amino-terminal pro-brain natriuretic peptide (NT-proBNP), carotid IMT, electrocardiography, ejection fraction and diastolic dysfunction (*E*/*A* ratio) in echocardiography. In RA patients in comparison with controls, there were significantly greater values of carotid IMT [0.83 (0.21) vs 0.62 (0.1) mm, $p < 0.001$], as well as higher incidence of atherosclerotic plaques [43 (61.4%) vs 10 (30.3%), $p = 0.003$], and prolonged QTc interval [439.6 (23.7) vs 414.0 (27.9) ms, $p < 0.001$]. The authors also demonstrated high or very high Systemic Coronary Risk Evaluation (SCORE) in 32.9% of patients with RA and increased serum NT-proBNP in 71.4%. The mean values of CV parameters (carotid IMT, E/A, NT-proBNP, SCORE) were associated with age, disease duration, rheumatoid factor (RF-IgM), and erythrocyte sedimentation rate. Therefore, the authors concluded that RA with continued low disease activity is associated with atherosclerosis and heart dysfunction [12]. These results demonstrated acceleration of atherosclerotic changes in RA patients with continued low disease activity compared with controls, findings that are in accord with those of Dehghan P., *et al* [13]. Moreover, patients with higher DAS28, erythrocyte sedimentation rate, RF-IgM concentration and bone erosions had greater deterioration of CV parameters. However, other studies found in RA patients with low disease activity that carotid IMT was not increased compared to controls, and that it was not associated with RA disease characteristics [14-16].

Nevertheless, there is increasing recognition that RA carries a heightened CVD morbidity and mortality derived from a number of reviews and meta-analysis [17-22]. In a review that included 91,618 patients, CVD accounted for 39.6% of all deaths. A large population meta-analysis comprising 111,758 patients found a 50% increased risk of CVD death. Another meta-analysis of 14 observational studies concluded a 48% increased risk of incident CVD in patients with RA, with the risk of myocardial infarction being increased by 68%. A recent prospective population-based cohort study of CVD end-points showed that RA patients had higher rates of myocardial infarction (IRR: 1.43), unheralded coronary death (1.60), heart failure (1.61), cardiac arrest (2.26) and peripheral arterial disease (1.36) [17-22]. In the inflammatory milieu of RA, atherosclerotic plaques are particularly unstable and vulnerable to rupture.

This dreadful association in pathophysiology, clinical events and complications, and worsen outcome is accompanied with elevation of serum biomarkers of inflammation. Elevated levels of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), interleukin-6 (IL-6) and interleukin-1β (IL-1β) are found in both entities, namely, RA and CVD, with higher levels being present in RA [23-25]. These biological serum markers have been implicated in endothelial cell activation and dysfunction, a crucial step for pannus formation in the synovial tissue of the joints, and in the pathogenesis of significant alterations in the vascular endothelium and atherosclerotic CVD [26-28]. The response of both entities to the same pharmacological drug treatment also shows the intertwined association between these chronic diseases. The results of studies performing cytokine-targeted therapy provided proof-of-concept in vivo, confirming the role of the cytokines and inflammation in RA and atherosclerosis pathogenesis. These cytokine-targeted treatments decrease certain parameters of inflammation like hsCRP and erythrocyte sedimentation rate in both entities. For example, TNF-α blockade improved endothelial-dependent vascular function in RA patients [29]. In patients with coronary artery disease, anti-IL-1β therapy significantly reduced the rate of subsequent CV events, independent of lipid-lowering [30]. Furthermore, IL-6 receptor inhibition lessened the inflammatory response and release of troponin-T after acute MI [31]. Indeed, the availability of specific anti-inflammatory drugs for RA and anti-TNF therapies have been associated with not only decreases in CV fatalities, but also influenced disease severity and mortality post MI in RA patients. These findings strengthen the notion that a reduction of vascular inflammation in RA patients is associated to better clinical outcomes by decreasing atherosclerosis burden which results in improved endothelial function, plaque stabilization and post-MI remodeling.

In conclusion, CVD disproportionally affects RA patients and is currently the major cause of morbidity and mortality among RA patients. CVD appears as a detectable condition much earlier in the evolution of patients with RA and has been reported even before full clinical presentation and diagnosis of this chronic inflammatory disease. Chronic inflammation is now regarded as the driver of accelerated atherosclerosis in patients with RA, and it seems to be the major underlying pathogenic factor linking RA and CVD. This is associated with endothelial dysfunction, metabolic lipid alterations, hypercoagulability and initial atherosclerosis state with unstable plaque formation. Effective disease control seems to be essential to prevent atherosclerosis and its consequences in RA patients. The use of disease modifying anti-rheumatic drug therapy, and biologic agents has been shown to control not only RA but also CVD risk. Early diagnostic detection,

the employment of carotid IMT, and aggressive management of CVD should be utilized in this high-risk population together with control of the traditional CVD risk factors. Hence, how helpful it is to know the presence of subclinical atherosclerosis in RA patients? Early clinical apprehension is paramount, the sooner the detection the greater the clinical benefits and outcomes. We should strive to get to know the presence of subclinical atherosclerosis in RA patients. The endeavor´s outcome is worth the sacrifice. Future exploration of the multiple immune and inflammatory pathways may identify new targets for therapeutic management to straighten the residual inflammatory risk that persists beyond the adequate management of traditional risk factors. Further research is needed to help characterize and establish the optimal diagnostic and therapeutic management strategies in this highly vulnerable population with rheumatoid arthritis.

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