Inflamed Joints and Stiff Arteries

Is Rheumatoid Arthritis a Cardiovascular Risk Factor?

Arshed A. Quyyumi, MD

Inflammation is currently considered to be the leading potential unifying mechanism that explains cardiovascular risk in RA. Atherosclerosis is characterized by a vascular inflammatory process mediated by mononuclear cell infiltration, elaboration of cytokines, increased cellular adhesion, and plaque destabilization, leading to a low-grade systemic inflammatory response that is an indicator of increased future risk of atherothrombotic events. In contrast to this low-grade inflammatory state observed in atherosclerosis, a more severe inflammation of the synovium characterizes RA, where the accompanying systemic inflammation often leads to a far more intense, 3- to 100-fold-greater elevation of cytokines such as TNF-α, interleukin-6, interleukin-1β, and C-reactive protein (CRP). The circulating levels of these cytokines reflect disease activity and duration and can be modified by a variety of antiinflammatory and disease-modifying therapies used in RA. Because several studies have shown an additive impact of disease activity, CRP levels, and sedimentation rate on cardiovascular disease in RA, it has been proposed that elevated cytokines might not just reflect increased risk, but, through their pleiotropic effects, directly exacerbate vascular disease. In favor of this argument is the potential for these cytokines to alter function in distant tissues including skeletal muscle handling of glucose leading to insulin resistance, altering adipose tissue metabolism of lipids leading to an atherogenic lipid profile, stimulation of the liver to release plasminogen activator inhibitor-1 and fibrinogen that enhance a prothrombotic state, and activation of the vascular endothelium.

The burden of vascular atherosclerotic disease and its abrupt progression to life-threatening manifestations such as death and myocardial infarction are not tightly linked. Thus, processes that initially lead to atherosclerotic plaque development and subsequently to plaque vulnerability, rupture, and acute cardiovascular events, although sequentially related, are highly unpredictable. Therefore, risk factors may either cause accelerated development of atherosclerotic plaque or predispose preexistent plaque into becoming unstable, provoking an atherothrombotic event. In addition to the distinctly higher risk of cardiovascular events, recent studies demonstrate that subclinical atherosclerosis and its surrogate functional measures, such as endothelial dysfunction and arterial stiffness, are also more prevalent in patients with RA.

Structural vascular disease, assessed either as carotid intima-media thickening or carotid plaque, is a strong predictor of adverse cardiovascular events. In a recent study in 98 consecutive RA patients and matched control subjects, there was a 3-fold increase in carotid atherosclerotic plaque, a finding that has not been uniformly observed previously. Similarly, 2 functional measures of vascular disease, endo-
thelial dysfunction and arterial stiffness, appear to predict future development of atherosclerosis and adverse cardiovascular events. Because inflammatory marker elevation in RA is a nonspecific signal, largely reflective of joint inflammation, these more specific vascular markers may potentially provide a better index of cardiovascular risk in RA. Endothelial dysfunction, estimated as elevated circulating levels of biomarkers of endothelial activation such as vascular cell adhesion molecule-1 and intercellular adhesion molecule, was observed in RA, and the levels of these biomarkers correlated with cardiovascular risk factors, inflammatory markers, and disease activity scores. This has been confirmed by using traditional techniques such as brachial artery flow–mediated vasodilation or intra-arterial infusions of acetylcholine, indicating that accelerated atherosclerosis may be driven by injury to the endothelial layer and that estimation of endothelial function may provide an early measure of vascular risk.

It now appears that endothelial dysfunction and atherosclerosis are a result of an imbalance between vascular damage and repair, where vascular injury is triggered by exposure to risk factors and repair is mediated by endothelial progenitor cells (EPCs). Vascular repair is achieved, at least in part, by bone marrow–derived EPCs that circulate in the bloodstream and home to areas of vascular injury, where, largely by paracrine mechanisms, they contribute to reendothelialization. The number and migratory activity of EPCs are reduced in patients with risk factors and in those with endothelial dysfunction or established atherosclerosis. Conversely, stimulation of progenitor cells can improve endothelial function and potentially retard atherosclerosis. In this context, it is intriguing that EPC activity was noted to be lower in patients with active RA, compared with those with inactive disease or healthy control subjects. Moreover, EPC counts were inversely related to disease duration and severity. This suggests that impaired endothelial repair may be an additional contributor to the endothelial dysfunction and rapid atherosclerotic progression in subjects with active RA.

More recently, arterial stiffness assessments have gained popularity as measures of subclinical vascular disease, particularly as data have accumulated that increased arterial stiffness is also a predictor of cardiovascular disease. Arterial stiffness can be quantified by using application tonometry and high-fidelity recordings of the carotid and radial arterial waveforms. This allows measurement of pulse-wave velocity (PWV) and generation of central aortic waveforms by means of a validated transfer function, as in the accompanying article by Mäki-Petäjä et al. As large arteries stiffen with age or disease processes, the PWV and amplitude of the reflected wave both increase. The reflected wave appears in the aorta during systole as opposed to diastole (in healthy subjects), augmenting central aortic pressure. Both PWV and the augmentation of the central aortic pressure, expressed as augmentation index (Alx), can be measured as indexes of arterial stiffness.

Increased arterial stiffness in patients with RA, measured either as an increase in Alx or PWV, has been reported, but the findings have varied between studies, possibly a reflection of differences in the age and demographics of the patients studied. Nevertheless, there is good agreement from these reports that arterial stiffness is increased such that the arterial tree develops a level of stiffness in RA that is observed in control subjects 20 years older. Arterial stiffening correlates with age and certain risk factors such as blood pressure and glucose but also with current inflammation measured as CRP or interleukin-6 levels. Interestingly, the duration of disease appeared to be a predictor for increased Alx previously but was not a predictor of increased PWV in the report by Mäki-Petäjä et al. This relation between elevated CRP levels and abnormal PWV and pulse pressure has been observed in healthy subjects and allows one to speculate that a heightened inflammatory status can in itself lead to increased arterial stiffness. This contention is further supported by the observation in the report by Mäki-Petäjä et al that TNF-α antagonist therapy reduced inflammation and simultaneously improved endothelial function and PWV. The mechanism by which systemic or remote inflammation causes increased central arterial stiffness remains an important area of future investigation.

The concept that RA is a cardiovascular risk factor is thrown into question when the confounding direct influence of drugs used to treat RA on cardiovascular risk factors is considered. Corticosteroids, for example, exacerbate dyslipidemia and blood pressure and adversely affect glucose metabolism, but they also reduce inflammation, making their net effect on vascular risk variable. Cardiovascular risk was much higher in patients treated with aggregate larger compared with smaller doses of corticosteroids, and the former had greater incidence of carotid plaque and arterial stiffness. Similarly, nonsteroidal anti-inflammatory agents may exacerbate hypertension, and COX-2 antagonists are associated with increased risk of myocardial infarction. In contrast, disease-modifying antirheumatic drugs (DMARDs) may be protective against cardiovascular risk. Not only does methotrexate effectively abate joint inflammation and reduce systemic inflammatory markers, but it may reduce myocardial infarction frequency by almost 70%. This is supported by tantalizing data indicating a significant reduction in cardiovascular mortality rates in the past compared with the previous decade, when there was a dramatic increase in use of DMARD therapy, particularly methotrexate.

TNF-α antagonist therapy may improve endothelial dysfunction, and in the study by Mäki-Petäjä et al, arterial stiffness simultaneous with a reduction in systemic and joint inflammation. However, whether this will translate into true reduction in cardiovascular risk remains unknown. In the absence of randomized, controlled trials designed to investigate cardiovascular risk with different treatment strategies in RA, observational studies demonstrating altered event rates with different therapeutic strategies may not only reflect the effect of individual drugs but also the impact of more extensive or severe disease that mandates use of these drugs. Separating these confounding effects will be crucial to development of rational recommendations for managing cardiovascular risk in RA. Although surrogate markers such as endothelial dysfunction, arterial stiffness, and carotid atherosclerosis appear to herald future risk of atherosclerotic disease, it is not certain whether they will also be faithful
markers of cardiovascular risk when evaluating treatment strategies. It is critically important to include these markers as well as biomarkers of inflammation and oxidative stress in future randomized trials in patients with RA to establish whether these markers continue to track with cardiovascular risk.

Despite these shortcomings, the recently established clinical practice guidelines on cardiovascular risk in RA offer a useful framework for reducing cardiovascular risk in patients. Both cardiologists and rheumatologists need to appreciate that patients with RA, who constitute up to 1% of the population, are at increased cardiovascular risk. Careful monitoring and aggressive treatment of risk factors are required, akin to what has been proposed for diabetics. Subjects at increased risk may be detected by measurement of inflammation and other early markers of vascular disease such as arterial stiffness. Glucocorticoids should be used in minimal effective doses, and DMARD therapy, particularly such as methotrexate, may improve cardiovascular risk. How-ever, whether early aspirin therapy, aggressive statin use, angiotensin inhibition, or TNF-α antagonists are indicated for reduction in cardiovascular risk in patients with RA remains to be investigated.

Disclosures

None.

References


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