THE SIGNIFICANCE OF ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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Abstract: In this article you can read about rheumatoid arthritis (RA) patients are at higher risk of accelerated atherosclerosis.

Key words: atherosclerosis rheumatoid arthritisendothelial dysfunctionerythrocyte sedimentation rate, antirheumatic agents brachial artery endotheliumc-reactive protein morbidity, tumor necrosis diameterfluid flow.

The systemic autoimmune disease rheumatoid arthritis (RA) is characterized by increased cardiovascular mortality and morbidity and is an independent cardiovascular risk factor. Cardiovascular diseases (CVDs) result from accelerated atherogenesis, which is a consequence of endothelial dysfunction in the early stages of the disease. Endothelial dysfunction is a functional and reversible alteration of endothelial cells and leads to a shift in the properties of the endothelium towards reduced vasodilation, a pro-inflammatory state, and proliferative and prothrombotic properties. In RA, endothelial dysfunction can occur in the large vessels (such as the conduit arteries) and in the small vessels of the microvasculature, which supply oxygen and nutrients to the tissue and control inflammation, repair and fluid exchange with the surrounding tissues. Growing evidence suggests that microvascular endothelial dysfunction contributes to CVD development, as it precedes and predicts the development of conduit artery atherosclerosis and associated risk factors. As such, numerous studies have investigated microvascular endothelial dysfunction in RA, including its link with disease activity, disease duration and inflammation, the effect of treatments on endothelial function, and possible circulating biomarkers of microvascular endothelial dysfunction. Such findings could have important implications in the cardiovascular risk management of patients with RA.

The recognition that rheumatoid arthritis (RA) patients are at a heightened risk of cardiovascular disease (CVD) events and mortality now spans more than two decades. During this period, much has been learned about the magnitude of the problem. In a large meta-analysis of 24 cohort studies [1], CVD mortality was 50% higher in RA compared with non-RA populations. Similarly, the relative increase in the risk of myocardial infarction (MI) and stroke was 68% and 41%, respectively [2]. Independent of atherosclerotic ischemic heart disease, RA patients are also at a heightened risk of myocardial dysfunction [3] and overt heart failure [4]. CVD is the primary cause of death in RA patients [5], and as CVD events, such as MI and stroke, tend to occur at

an earlier age in RA compared with the general (non-RA) population, life expectancy is reduced.

Premature CVD is a contributor to the widened mortality gap observed between RA and non-RA populations [6]. Although there are some indications that this gap may be closing with the widespread adoption of early and aggressive treatment strategies [7], not all recent studies demonstrate the same promising trend [8], suggesting that CVD in RA remains a significant public health problem.

Reducing CVD event rates and mortality in RA requires the identification of susceptible subgroups and high-impact causal determinants. A substantial number of observational epidemiologic studies have sought to identify the RA-specific characteristics associated with CVD risk factors (traditional, nontraditional, and inflammatory), intermediate measures (i.e., atherosclerosis and atherothrombosis), and CVD events in RA. However, it is important to understand that these studies identify associations only, and, despite the number of studies that have been conducted, an incomplete understanding of causal determinants remains. Consistency and temporality are among the primary criteria for arguing causality in observational studies. However, there is notable heterogeneity in the factors identified as associated with RA CVD across studies, which may in part be explained by differing outcomes, populations, and exposure periods studied. Few are longitudinal, and among those that are, follow-up times are often limited, making the assessment of the association of exposure to outcome problematic. In addition, many combine RA patients at varying stages of disease, limiting the ability to identify subgroups of RA patients at heightened risk. Most rely on single point in time assessments of CVD risk factors and articular/systemic inflammation, which is problematic in a disease in which substantial time variance in risk factors is expected, both as a natural function of disease fluctuation and with treatment. It is not surprising, then, that our understanding of the determinants of CVD in RA remains limited.

Even with consistency and temporality demonstrated across multiple observational cohorts, more is required to justify health policy recommendations. Here, trials are essential to provide evidence that specific interventions affect outcomes. Unfortunately, there are few trials evaluating the efficacy of specific interventions for either primary or secondary prevention of CVD in RA, and none evaluating the effectiveness of preventive strategies in the setting of the delivery of RA clinical care. The scarcity of these trials is understandable given that (1) causal determinants from observational studies on which to base trials are uncertain, (2) trials with CVD events as outcomes often require large numbers (i.e., thousands) of enrollees, and (3) although the most common autoimmune inflammatory arthritis, RA is still relatively uncommon in the general population, and many of the most severely affected (and thus potentially most at risk of adverse CVD events) are unable or unwilling to participate in clinical

trials. The recent Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in RA (TRACE RA) Trial (discussed subsequently) is testament to these challenges.

Tasked with caring for RA patients in 2015, what must the practicing rheumatologist do? Most will find it unacceptable to await definitive trials of CVD screening and treatment strategies specifically developed in RA populations, which remain years to a decade or more in the future. Short of these, extrapolations from observational studies of RA patients and trials of non-RA populations with some applicability to RA may provide some insight into areas for intervention. However, any recommendations based on lower levels of evidence require the consideration of possible adverse effects, which include not only direct adverse effects of testing and treatments but also indirect adverse effects, such as diverting resources and attention to interventions that may have no value. Even in the setting of known increased risk, current practice for treating CVD risk factors in RA patients is generally poor.

This review focuses on studies exploring determinants of CVD risk factors, intermediates, and events in RA, and studies evaluating CVD screening and treatment strategies for clinical practice. Current expert-opinion-based recommendations are discussed, with the current level of evidence reviewed in the context of a research agenda targeting a more rigorous approach to primary and secondary CVD screening and prevention in RA. There is a paucity of literature regarding the screening and prevention of cerebrovascular disease and myocardial dysfunction in RA. As such, this review concentrates on coronary and extra-coronary atherosclerosis as it pertains to the prediction of ischemic heart disease events.

References

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