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Cardiovascular disease (CVD) is a major cause of morbidity and mortality in rheumatoid arthritis (RA). Enhanced rates of incident CV events in RA are evident even before signs and symptoms of arthritis begin, suggesting that RA-specific immune-mediated processes that promote CV risk are activated very early. We hypothesized that genetic risk (present at birth) and/or RA-specific autoantibodies (known to predate clinical symptoms) may convey early risk for coronary artery disease (CAD) and/or heart failure (HF) in RA. Indeed, our preliminary data strongly suggest that RA susceptibility genes (the HLA-DRB1* "shared epitopes") are predictive of more severe subclinical atherosclerosis in RA. Furthermore, RA patients exhibited a markedly lower left ventricular (LV) mass than matched controls, and, among the RA patients, this was highly associated with anti-cyclic citrullinated (- CCP) peptide antibodies. This is in stark contrast to an increase in LV mass that generally precedes clinical HF in the general population, and suggests that HF in RA may progress along different pathways. In pilot studies, we have also observed diffuse sub-endocardial hypoperfusion in the LVs of 3 of 3 patients with active RA, suggesting that myocardial microvascular dysfunction is a key contributor to loss of LV mass. It has been hypothesized that effective treatment of RA may reduce the risk of HF in RA but a major RA therapy [the tumor necrosis factor-1 (TNF- 1) antagonists] appeared to worsen HF in non-RA patients. So far, no studies have directly investigated the effect of TNF antagonists on myocardial structure and function in RA. Our overall hypothesis is that RA-specific immune mechanisms initiate and/or propagate systemic, as well as local (myocardial), inflammation, leading to accelerated atherosclerosis and myocardial dysfunction. We propose the following three specific aims to investigate this hypothesis. Specific Aim 1. In combined (JHU and nonJHU) RA populations, we will evaluate the association of RA susceptibility genes/loci - with a primary focus on the HLA-DRB1 "shared epitope" genes - with the presence and severity of atherosclerosis. Specific Aim 2. In RA patients, we will evaluate the association of RA characteristics (particularly, anti- CCP), myocardial microvascular perfusion, and myocardial inflammation/fibrosis with parameters of LV structure and function. Specific Aim 3. In a prospective pilot study of RA patients without clinical HF, we will evaluate the effect of treatment with TNF antagonists on parameters of LV structure and function, and on myocardial microvascular perfusion and myocardial inflammation/fibrosis over six months. Our preliminary data represent novel findings that could have significant impact on early recognition and management of RA-associated CV disease. A better understanding of RA related factors that initiate and/or accelerate CAD and HF in RA, and that identify subgroups at highest risk, and of the effect of treatment on these risks, are crucial in order to develop targeted interventions and reduce CV associated morbidity and mortality.
