Atherosclerosis and Cardiovascular Disease in Rheumatoid Arthritis

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Atherosclerosis is an inflammatory disease, and the major cause of cardiovascular disease (CVD). This notion is based on the presence of immune-competent cells in atherosclerotic lesions in the intima of some arteries. Many of these cells — monocytes/macrophages, T cells, some mast cells, and even a few B cells and neutrophils — are activated, producing mainly proinflammatory cytokines^{1,2}. Of note, atherosclerosis *per se* is not believed to be the major cause of CVD, even though arterial narrowing can play a role. Instead, it is complications of atherosclerosis leading to rupture of atherosclerotic plaques that appear to be the main underlying factor, causing atherothrombosis as manifested by myocardial infarction (MI) and stroke².

Similarities between atherosclerosis and autoimmune diseases are indicated by studies in which adoptive transfer of β_2 -glycoprotein I-reactive lymphocytes increases atherosclerosis in mouse models of atherosclerosis³. Further, the immune system can influence atherosclerosis development: immunization with heat shock protein 60/65 increases atherosclerosis⁴, while the opposite is the case if oxidized low-density lipoprotein is used⁵.

It is interesting that the connection between inflammation and atherosclerosis was reported more than a century and a half ago by the Austrian pathologist Karl von Rokitansky, who described what can be inferred as inflammatory changes in atherosclerosis. This was also noted by the famous German pathologist Rudolf Virchow, who was also a pioneer in social medicine. These researchers had somewhat differing opinions about the nature of the disease. While Rokitansky thought the inflammation was secondary, Virchow believed it was mainly primary⁶. Both appear to have been right, because inflammation is a major characteristic of atherosclerosis *per se*², while rheumatic inflammatory diseases confer increased risk of both atherosclerosis and CVD^{7,8}. Thus, the increased risk of atherosclerosis and CVD in rheumatic disease is not only a clinical problem. Studies of these associations could also raise the understanding of the conditions themselves.

In systemic lupus erythematosus (SLE), the risk of CVD

is higher, even 50 times higher, according to one study⁹. A combination of traditional and nontraditional risk factors appear to account for the raised risk of CVD in SLE^{7,10}. Further, atherosclerosis, at least in the form of atherosclerotic plaques, is increased in several studies. In SLE, carotid intima-media thickness (cIMT) in general is not raised in some studies^{7,10}. Other measures of atherosclerosis, such as the prevalence of echolucent plaques (reported to be more vulnerable), are raised in SLE¹¹. Alternative measures besides cIMT should thus be investigated in rheumatic diseases such as SLE.

The situation appears to be less clear in rheumatoid arthritis (RA) than in SLE. While the risk of CVD is raised in many studies¹², the increase is not as high as in SLE. Some authors have reported increased risk comparable to diabetes type 2¹³, but there are differences in results depending on stage of disease and other factors. Evidence indicates that, as in SLE, traditional risk factors such as dyslipidemia, hypertension, diabetes, and smoking play a role. In addition, nontraditional risk factors add to the risk burden⁷. We recently reported that antibodies against phosphorylcholine (anti-PC) could be of importance as independent protection markers in atherosclerosis and CVD in the general population. Mechanisms include antiinflammatory properties and decreased uptake of oxidized lipoproteins in the arterial wall. In SLE, antiphospholipid antibodies and low anti-PC levels⁷ are examples of nontraditional risk markers, while low anti-PC is a risk marker also in RA for atherosclerosis, CVD, and being a nonresponder to biologics^{14,15,16}.

Another problem, especially in RA (and potentially many other inflammatory conditions), is the use of nonsteroidal antiinflammatory drugs (NSAID), which is so common that it is very difficult to control for. NSAID in general, not only cyclooxygenase-2 inhibitors, are associated with increased risk of CVD, which is most likely related to thrombosis, although the effects on atherosclerosis development are little known¹⁷. It is not clear how large a part of the increased risk of CVD in RA could be

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attributed to NSAID use. Therefore detailed studies of the properties of arteries and atherosclerosis in RA are very important, because it is most likely (although not certain) that NSAID mainly act by influencing thrombosis risk¹⁷.

In this issue of the *Journal of Rheumatology*, van Sijl, *et al*¹⁸ report that patients with RA differ from healthy controls in carotid arterial wall remodeling, which is believed to be a response to hemodynamic and/or metabolic factors. This remodeling may be maladaptive if stress on the arterial wall increases too much^{19,20}. Maladaptive outward modeling is also prospectively associated with clustering of risk factors²¹ and may be related to plaque vulnerability²². There was no difference in cIMT between patients with RA and controls. However, measures of vascular remodeling such as circumferential wall stress and circumferential wall tension were calculated. The authors conclude that RA is associated with maladaptive outward carotid arterial remodeling, which could enhance the risk of CVD in RA even though cIMT was not raised.

This finding adds to the knowledge of atherosclerosis in rheumatic disease, and could contribute to our understanding of how CVD could ensue even though cIMT is not increased.

Further studies are needed to shed more light on the detailed properties of atherosclerosis and mechanisms and risk factors in plaque rupture in rheumatic diseases to improve prevention and treatment.

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