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REVIEW

Cardiovascular co-morbidity in patients with rheumatic diseases

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Abstract

During recent years atherosclerosis, the major cause of cardiovascular disease (CVD), has been recognised as a chronic inflammatory condition in which rupture of atherosclerotic lesions appears to play a major role. The risk of CVD is raised in many rheumatic diseases. This risk is high in systemic lupus erythematosus – as much as a 50-times increase among middle-aged women has been reported. Studies on CVD and atherosclerosis in rheumatic disease could thus provide interesting information about CVD and atherosclerosis in addition to being an important clinical problem. A combination of traditional and nontraditional risk factors accounts for the increased risk of CVD and atherosclerosis in rheumatic disease. One interesting possibility is that atherosclerotic lesions in rheumatic disease are more prone to rupture than normal atherosclerotic lesions. It is also likely that increased risk of thrombosis may play an important role, not least in systemic lupus erythematosus. Further, it is not clear whether an increased risk of CVD is a general feature of rheumatic disease, or whether this only occurs among subgroups of patients. It should be emphasised that there is an apparent lack of treatment studies where CVD in rheumatic disease is the end point. Control of disease activity and of traditional risk factors, however, appears to be well founded in relation to CVD in rheumatic disease. Further studies are needed to determine the exact role of lipid-lowering drugs as statins. Hopefully novel therapies can be developed that target the causes of the inflammation in atherosclerotic lesions both in rheumatic patients and in the general population.

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Introduction

The history of ideas and hypotheses about atherosclerosis is interesting. The inflammatory nature of atherosclerosis and the involvement of immune competent cells was described by the Austrian pathologist Karl Rokitansky in the 1840s and by the pathologist and social medicine pioneer Rudolf Virchow somewhat later in the 1850s [1]. As discussed in a previous editorial [2], these two important persons in the history of medicine had an interesting argument: Rokitansky believed that the inflammation in atherosclerosis was secondary to other disease processes, but Virchow instead suggested that atherosclerosis is a primary inflammatory condition. The relevance of this discussion to cardiovascular disease (CVD) and atherosclerosis in rheumatic disease is obvious, and in fact both arguments were most probably right. Virchow clearly had a point verified in an interesting paper based on studies of Rokitansky's own arterial pathological specimens. Here, activated T cells and other inflammatory and immune competent cells are present already at a very early stage of disease, which in principle adds support to Virchow's opinions [1]. A recent meta-analysis indicates that rheumatic diseases raise the risk of premature atherosclerosis, implying that inflammatory conditions such as in rheumatic diseases could have secondary atherosclerosis as a side effect [3]. Both Rokitansky and Virchow were right, in a non-mutually exclusive way.

It was not until the early 1980s that the inflammation/immune hypothesis in atherosclerosis surfaced [4,5], although Russell Ross came close 1977 with his response to injury hypothesis [6]. Before that, the field was dominated by the lipid hypothesis – attention was paid especially to cholesterol in the blood as a risk factor. Initially, it appeared that these two ideas about the nature of the disease contradicted each other, but now there appears to be consensus that both are relevant and nonmutually exclusive, and each probably plays a different role depending on patient groups.

Interestingly, statins can illustrate this dual nature of atherosclerosis and CVD. Statins are, from a commercial point of view, among the most successful medicines in history. In fact, they may be beneficial not only due to the

mechanism for which they were developed but, in addition, for pleiotropic effects including anti-inflammatory effects (caused by influencing prenylation among other processes), antioxidant effects, decreasing low-density lipoprotein (LDL) oxidation, and even immune modulatory effects, decreasing MHC class 2 interaction with antigen [7]. The Jupiter study recently demonstrated that statin treatment may be beneficial for individuals with raised high-sensitivity C-reactive protein but normal LDL [8].

The nature of atherosclerosis and cardiovascular disease

Atherosclerosis is an inflammatory process in large and middle-sized arteries, where activated monocytes/macrophages and T cells are present in the intima [9,10]. Proinflammatory cytokines are produced by immune competent cells in the lesions [9-11]. In addition to chronic inflammation, atherosclerosis also shares characteristics with autoimmune diseases – as indicated by studies where adoptive transfer of β_2-glycoprotein I-reactive lymphocytes enhances atherosclerosis in animal models [12].

Of note, atherosclerosis *per se* is widespread in the population. Atherosclerosis has been detected in Egyptian mummies, and also in young adult humans. Further, and surprisingly, even foetal atherosclerosis in the form of early changes (fatty streaks) has been determined [13]. One could therefore debate whether atherosclerosis indeed is a disease and not a normal aspect of human aging.

Even though narrow lumens caused by noncomplicated atherosclerosis may be a problem in some cases, however, it is the development of atherosclerotic plaques into more complicated lesions – where fissures and even microthrombae and eventually plaque rupture occur – that leads to CVD, including stroke and acute coronary syndrome, heart failure (as a later consequence of acute coronary syndrome), and claudication. One major issue is therefore the cause of plaque rupture. Inflammation plays a major role, although the exact mechanisms are not known. Activation of proinflammatory cytokines and chemokines are prominent features of plaque rupture. One interesting possibility is therefore that the proinflammatory state in rheumatic disease *per se* may promote atherosclerotic plaque rupture.

An interesting development is the possibility of immunisation, active or passive (administering antibodies), against atherosclerosis and/or CVD. Not unexpectedly, LDL is a target – examples of antigens as culprits include apolipoprotein B peptides [14] (apolipoprotein B being the major carrier protein in LDL) or antigens in the phospholipid moiety such as phorphorylcholine (PC). Natural IgM antibodies against PC (anti-PC) are negatively associated with human atherosclerosis [15] and low levels of anti-PC predict increased risk of CVD independent of other risk factors [16-18].

In the above-mentioned meta-analysis where rheumatic disease and atherosclerosis were determined, it was demonstrated that there is indeed a premature atherosclerosis in general. In this study, cases and matched controls where identified through systematic analysis on PubMed and 68 comparisons from 60 different studies were made. Taken together, of patients included in this meta-analysis, 37% had rheumatoid arthritis (RA), 35% had systemic lupus erythematosus (SLE), 9% had systemic sclerosis, and 19% had other rheumatic diseases [3].

In both SLE and RA, an association between CVD and extent of atherosclerosis has been established [19,20]. This association points to atherosclerosis as a major underlying factor in co-morbidity between rheumatic diseases (at least SLE and RA) and CVD.

Systemic lupus erythematosus

Since the inflammatory nature of atherosclerosis was not in focus until the 1980s, it is not surprising that little attention was paid to associations between CVD and rheumatic disease. In an early report from 1976, however, a bimodal pattern of SLE was reported [21], According to this paper, in addition to early direct effects of SLE on various organ systems, a later complication was CVD [21].

Before immunosuppressive treatment was implemented, more acute SLE manifestations, such as nephritis, were often fatal. Early autopsy and angiographic studies also demonstrated that the prevalence of atherosclerotic lesions is high in SLE [22,23].

The strong association between SLE and CVD has been firmly established in many reports. This risk can be very high in some patient groups: according to one study, women aged 44 to 50 had a 50-times increased risk of myocardial infarction [24]; and an increased CVD risk in SLE is well documented [25]. Indeed, T-helper type 2 cytokines have been associated with SLE and at the same time inhibit atherosclerosis in experimental animals [25]. Even though it is clear that the risk of CVD is raised in SLE, this possibly only applies to a subgroup of SLE patients. Information and advice for rheumatic patients in relation to CVD risk should take this possibility into account. Even though CVD is associated with atherosclerosis in SLE [20], thrombosis *per se* possibly adds to the risk [20].

A combination of traditional and nontraditional risk factors typically accounts for, statistically, the increased risk of CVD in SLE, although there are variations in studies – for example, in relation to the role of smoking. Dyslipidaemia (typically the lupus pattern with high triglycerides), hypertension and renal disease are in most studies significantly associated with CVD risk.

Nontraditional factors such as inflammation and antiphospholipid antibodies (aPL) are also of importance in SLE, aPL more than in other rheumatic diseases. LDL is generally recognised as a risk factor in the general population, and LDL oxidation is believed to be of importance due to its proinflammatory, even toxic, effects and the uptake of oxidised LDL into the vascular wall, from which it is then not removed. It is therefore of interest that oxidised LDL in the circulation is raised in SLE [20,25].

A possibility deserving further study is that atherosclerotic plaques in SLE are more prone to rupture. We recently determined by carotid ultrasound that vulnerable atherosclerotic plaques are more prevalent in SLE, lending support to this notion [26].

Emerging risk factors that also implicate novel mechanisms may play a role in SLE-related CVD. Two examples of this are, firstly, anti-PC and, secondly, the binding of annexin A5 and interaction with endothelial cells, aPL and inflammation.

Firstly, we reported recently that low levels of anti-PC independently predict CVD in general and that there is a negative association between anti-PC levels and development of human atherosclerosis, where high levels confer decreased atherosclerosis development after 5 years [27]. Further, low levels of anti-PC were associated with SLE in a nested case–control SLE study [28] – and in a new SLE case–control study we confirmed and extended this association, low levels of anti-PC being associated with prevalence of atherosclerotic plaques [29].

Mechanisms by which anti-PC could be beneficial include an anti-inflammatory effect whereby anti-PC inhibits endothelial activation caused by inflammatory phospholipids [28]. In principle, by this anti-inflammatory effect, low anti-PC could predispose to both atherosclerosis and rheumatic disease, suggesting one possible common underlying factor. Another mechanism could be decreased uptake of oxidised LDL in macrophages, which could lead to less atherosclerosis development [16].

Secondly, binding of annexin A5, which has antithrombotic properties, is decreased in individuals with SLE and CVD. This decreased binding is caused by aPL that outcompete annexin A5 binding, causing a prothrombotic state. We also demonstrated that annexin A5 is abundant in atherosclerotic plaques, at sites prone to plaque rupture, and suggested that this protein may stabilise plaques, protect endothelium and inhibit plaque rupture [30]. Further, pooled immunoglobulin (intravenous immunoglobulin; IVIG) can neutralise aPL and restore binding of annexin A5 [31].

Rheumatoid arthritis

The risk of CVD is also increased in RA, although not as strikingly as in SLE [32-35]. The risk varies in different studies, which could depend on the study populations chosen, age and other factors, including secular trends for RA *per se*. As in SLE, a combination of traditional and nontraditional risk factors, including inflammation and also extra-articular manifestations, appears to explain this increased risk [32-34,36-41].

For example, in young women a 3.6-times increased risk of death in coronary artery disease was reported, and in a population-based cohort of RA patients the incidence of myocardial infarction and coronary heart disease was 50% higher in RA [32]. Similar results were obtained in other studies [42], and it has been suggested that RA is comparable with type 2 diabetes mellitus as an independent risk factor for CVD [43]. As in SLE, traditional CVD risk factors and inflammation-associated factors appear to be of major importance to explain the increased risk of CVD in RA [25]. The risk of CVD in RA may be decreasing [44].

While it thus appears that CVD is increased in RA and SLE (and other rheumatic diseases), the exact role of atherosclerosis/CVD and potential underlying mechanisms in RA has been less clear [25].

The role of rheumatoid factor in this context is not known, although interestingly rheumatoid factor is often present in smokers. Further, it is not clear how immune complexes in general, or even complement, affect RA-related cardiovascular co-morbidity. Perhaps complement could play a different role depending on the disease stage.

Another interesting development in RA is the role of citrullinated proteins and antibodies against these. Recent findings imply that such antibodies, increasingly recognised as important novel risk markers for RA, could also play an independent role in RA-related atherosclerosis and CVD, including ischaemic heart disease [45,46].

In an interesting paper, functional polymorphisms relating to MHC-molecule expression were demonstrated to be associated with susceptibility to RA, multiple sclerosis and myocardial infarction [47], suggesting putative common mechanisms.

While many studies including the above-mentioned meta-analysis support an increased prevalence of atherosclerosis as determined by ultrasound of carotid arteries [37,39,48], there are also studies where such an increase was not detected, either as the intima-media thickness or as prevalence of plaque [36]. In favour of arterial changes in RA (as in SLE) are studies in which endothelial dysfunction has been reported [49]. aPL and also antibodies against oxidised LDL are raised in RA but their clinical importance for CVD and atherosclerosis is not clear [50]. Lipid peroxidation may also play a role in RA, and oxidised LDL-containing foam cells have been described in RA synovia [51]. Further, oxidative stress is increased in RA and associated with atherosclerosis [52].

Another emerging factor in CVD is heat shock proteins, which are implicated in both RA and atherosclerosis – although immune reactivity to heat shock proteins in RA appears to play a somewhat different role, being protective in many cases while it appears to be unfavourable in atherosclerosis and CVD [53].

Dyslipidaemia is often present in RA with low high-density lipoprotein and high triglycerides in a similar way as in inflammatory and infectious diseases in general. An increased prevalence of potentially atherogenic, small, dense LDL particles were reported in RA, and LDL from RA patients also has an increased capacity to bind proteoglycans, which most probably is an important step in early atherogenesis [54].

As in SLE, the role played by treatment is of potential importance. Corticosteroids at moderate dose (7.5 mg prednisolone) did not affect atherosclerosis, but it is still possible they would affect atherosclerosis in higher doses – for example, the unfavourable metabolic effects may outweigh the anti-inflammatory properties [55]. The role of methotrexate has been debated, but recent investigations suggest such treatment with folate substitution could influence CVD risk factors in a beneficial way [56].

TNF inhibition could be expected to be anti-atherogenic since TNF has proinflammatory and unfavourable metabolic effects [20]; in line with this, in a mouse model of atherosclerosis, TNF inhibition decreased atherosclerosis development [57]. Side effects such as heart failure are implicated [58]. In humans, however, TNF inhibition appears to have a favourable effect on CVD [59].

Even though statins may be implicated in RA (and potentially other rheumatic diseases) and indeed have an effect on RA *per se* [60], further studies are needed before general recommendations should be given.

Other rheumatic diseases and atherosclerosis/ cardiovascular disease

SLE and RA in relation to atherosclerosis and CVD have been studied more than other rheumatic diseases. In psoriatic arthritis, increased atherosclerosis has been reported [61,62] and an increased prevalence of CVD is well established with risk factors comparable with those in RA [63]. In ankylosing spondylitis, studies indicate that the risk of CVD is enhanced, but perhaps less so than in RA and SLE. Also in ankylosing spondylitis, dyslipidaemia and inflammation *per se* may play a role, and positive effects of TNF inhibitors are discussed [64-66].

In vasculitis, increased atherosclerosis has been noted both in Kawasaki's disease [67] and Takayasu's arteritis [68,69]. In Behçet's disease, where vasculitis commonly occurs, and in Wegener's granulomatosis, increased atherosclerosis as determined by carotid ultrasound has also been reported [70,71].

Gout has been associated with CVD and increased urate levels, but urate may also have antioxidant properties that may be beneficial under some circumstances [72].

Summary and conclusions

Both atherosclerosis and the risk of CVD are increased in rheumatic diseases, especially in SLE, and the risk appears to be strikingly high. The underlying mechanisms are probably related to atherothrombosis and increased prevalence of atherosclerotic plaques where traditional and nontraditional risk factors act in concert. When treating patients with rheumatic disease, it is important to pay attention to the increased risk of CVD. Traditional risk factors as dyslipidaemia, hypertension, diabetes and smoking should be closely monitored and disease symptoms including inflammation should be treated. Hopefully novel therapeutic modalities will be developed that target the causes of the inflammation present in atherosclerotic lesions.

This article is part of the series *Comorbid conditions in subjects with rheumatic diseases*, edited by Daniel Aletaha and Thomas Dörner. Other articles in this series can be found at http://arthritis-research.com/series/comorbid

Abbreviations

anti-PC, natural IgM antibodies against phorphorylcholine; aPL, antiphospholipid antibodies; CVD, cardiovascular disease; LDL, low-density lipoprotein; PC, phorphorylcholine; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

Competing interests

The author declares that he has no competing interests.

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