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Inflammation: A pivotal link between autoimmune diseases and atherosclerosis ☆

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Abstract

Premature coronary heart disease has emerged as a major cause of morbidity and mortality in systemic autoimmune diseases. Recent epidemiologic and pathogenesis studies have suggested a great deal in common between the pathogenesis of prototypic autoimmune disease such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) and that of atherosclerosis. Some of the most remarkable data in support of a link between autoimmunity and atherosclerosis comes from epidemiological studies of patients with autoimmune disorders (RA and SLE). Many epidemiologic observations have linked systemic inflammation with the cardiovascular events in autoimmune disease such as RA and SLE. Inflammation is increasingly being considered central to the pathogenesis of atherosclerosis and an important risk factor for vascular disease. Systemic inflammation may be regarded as accelerating the atherosclerotic process. Systemic levels of soluble inflammatory mediators such as C-reactive protein (CRP) have been associated with cardiovascular risk in the general population. CRP, or more specifically high sensitivity-hsCRP, is a marker of systemic inflammation that has been identified as a valid biomarker of cardiovascular risk. Furthermore, the immunomodulatory and anti-inflammatory actions of statins may affect their utility in the context of chronic inflammatory autoimmune disease. Thus, effective control or dampening of inflammation, with such agents, should be included in the therapeutic armamentarium of autoimmune diseases with the aim of protecting against cardiovascular disease.

Keywords: Inflammation; Autoimmune diseases; Atherosclerosis

Contents

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1. Epidemiology of cardiovascular disease in prototypic autoimmune diseases (SLE and RA)—extent of the burden

Cardiovascular (CVS) diseases secondary to accelerated atherosclerosis are now accepted as a leading cause of morbidity and mortality in patients suffering from systemic autoimmune diseases [1,2]. Some of the most remarkable data that has come to surface linking autoimmunity and atherosclerosis stems from epidemiological studies of patients with autoimmune diseases. Patients having prototypic autoimmune disease such as SLE and RA have a significantly higher risk and increased prevalence of CVS disease compared with age–sex matched controls [3,4].

Patients with SLE are 5–6 times more likely to have a significant coronary event than people in the general population. This excess risk is especially pronounced in younger women where the risk may be increased by a factor of 50 [3].

RA, another prototypic autoimmune disease, is also associated with accelerated vascular risk resulting in early mortality and excess morbidity [5]. Several epidemiological studies have shown that the risk of a CVS event is doubled in RA patients irrespective of the traditional CVS risk factors, and is frequently silent and subclinical [6,7].

Compelling evidence shows that RA and SLE are independent risk factors for the development of atherosclerosis [6,7]. Furthermore, it was recently reported, in a case-control study, that RA may be an independent risk factor for multivessel coronary artery disease [8]. It has been suggested that prototypic autoimmune diseases such as SLE be considered like, diabetes mellitus, as coronary heart disease equivalent conditions [9].

2. Inflammation: a cardiovascular risk factor-cutting into the heart of cardiovascular affection

Epidemiological observations have linked inflammation with the cardiovascular events [10]. Clinical epidemiological observations strongly suggest that, together with classical conventional risk factors, other mechanisms (non-conventional/disease-specific factors) promote accelerated atherosclerosis in diseases like SLE and RA [7,11]. The excess risk observed in autoimmune disease appears to be driven by systemic inflammation, directly or indirectly through its damaging effects on the vasculature; and thus the concept of inflammation as a cardiovascular risk factor [12].

Data has shown that any type of chronic inflammation may act independently or together with non-traditional atherosclerotic risk factors [5,13].

RA and other autoimmune chronic inflammatory disorders may provide insight into these complex interactions between traditional and non-traditional/disease-related (including: inflammation, dyslipidaemia, homocysteine, oxidative stress, thrombotic variables, insulin resistance and autoantigens) risk factors.

The contemporary view of atherosclerosis has broadened to include an active and complex role for inflammation, orchestrated in part by mediators of the immune system, that is, atherosclerosis is seen as an active inflammatory and immune-mediated process in which systemic inflammatory and soluble immune mechanisms (circulating antibodies, immune complexes, complement activation products) play a role in accelerating vessel pathology [13,14].

Thus, although many factors cause atherosclerosis, inflammation at the site of vascular injury mediates atherogenesis. Recent advances in basic science have established the fundamental role for inflammation in mediating all stages of atherosclerosis and in precipitating a cascade of cellular and molecular responses that can, at best, be characterized as an inflammatory process exhibiting many equivalents to autoimmune diseases such as RA [13,14].

It is hence, not surprising that atherosclerosis develops in SLE and RA-autoimmune diseases characterized by chronic inflammation and immune disarray. In fact, many molecular and cellular mediators of inflammation found in RA and SLE are key to the development of atherosclerotic lesions.

3. Autoimmune disease and atherosclerosis: two diseases, one pathobiology

An increasing body of evidence supports that atherosclerosis shares many similarities with other chronic inflammatory autoimmune diseases such as RA [13].

Many parallels have emerged between the paradigm of inflammation in the pathogenesis of atherosclerosis and the mechanisms of inflammation in the pathogenesis of autoimmune diseases such as RA and SLE.

When comparing atherosclerosis to RA, a bone fide autoimmune disease, an interesting pattern of similarities can be deduced (Fig. 1), in that, both have evidence of activation of macrophages, B cells, T cells, and endothelial cells; alteration in the Th1/Th2 ratio and elevation of inflammatory cytokines [15].

This concept of inflammatory-driven atherosclerosis is consistent with the plaque composition of unstable coronary lesions, with an abundance of inflammatory and immune cells present at the shoulder region that act to erode the collagen cap. An appearance indistinguishable of that of inflammatory synovitis seen in RA, where many of the same cells seen comprising the inflammatory infiltrate in the RA joint lining are likewise found in the atherosclerotic plaque (Fig. 1). The similarities between RA and atherosclerosis and the shared pathobiology were highlighted several years ago. Both aberrant cellular and humoral immune responses are integral to the pathogenesis of the two conditions [13].

Distinct pathogenic mechanisms occur in individual autoimmune states. In RA, there is aberrant activity of $CD4^+$ T cells, B cells and cells of the monocyte/macrophage lineage. Th1 cytokines predominate [13,16].

T cells in patients with acute coronary syndromes (ACS) are skewed toward the production of interferon gamma (IFN-α), a potent monocyte activator largely derived from a distinct subset of $CD4^+$ T cells, that in contrast to classic $CD4^+$ T cells, lacks the costimulatory molecule, CD28 [17]. $CD4^+$ $CD28^{null}$ T cells are clonally expanded in ACS and invade the unstable atherosclerotic plaque. These cells contribute to reduced collagen synthesis and weakening of the fibrous cap [17]. Moreover, $CD4^+$ $CD28^{null}$ T cells have cytotoxic capability effectively killing endothelial cells in vitro, and may contribute to endothelial injury in coronary plaques [17]. Similarly, in patients with RA, a stable expansion of $CD4^+$ T cell subset that lacks expression of the CD28 molecule and that secretes predominantly Th1 cytokines (that promote endothelial injury) has been described in the peripheral blood and may contribute to early atherosclerotic damage in these patients [13,16–18]. This, in conjunction with the production of matrix metalloproteinases (enzymes released by activated macrophages and involved in collagen breakdown), play a crucial role in collagen degradation and joint destruction as well as destabilization and rupture of a vulnerable plaque [13].

Similarities between the inflammatory and immune-mediated mechanisms of both atherogenesis and SLE also exist.

The pathogenesis of CVS disease in SLE is multifactorial and complex, involving an interaction between inflammation-induced and auto-antibody-mediated vascular injury and thrombosis from the underlying disorder and traditional CVS risk factors [19]. SLE-related factors seem to be involved in all stages of atherosclerosis. Processes integral to the pathogenesis of SLE, including immune complex formation and complement activation are involved in endothelial injury and local inflammation. The upregulated CD40–CD40–ligand interactions in SLE may influence many processes, ranging from promoting inflammatory processes to contributing to thrombus formation [19]. The CD40–CD40–ligand is another immune-mediated interaction, common to both SLE and atherosclerosis that leads to upregulation of adhesion molecules on endothelial cells [19,20].

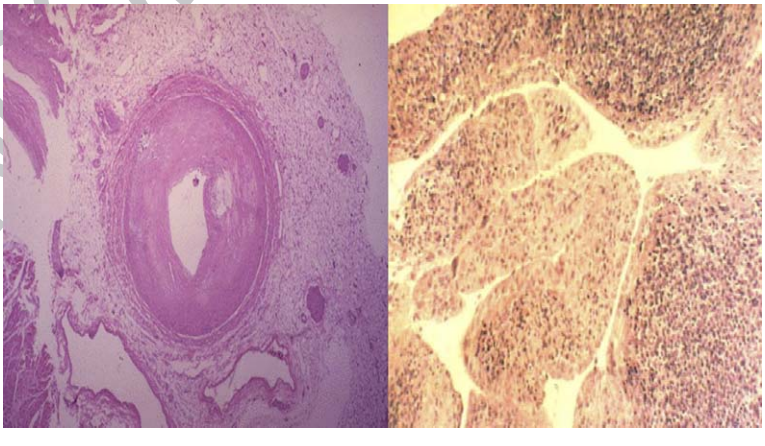

Fig. 1. Histopathological specimens depicting similar inflammatory cells in chronic synovitis of RA (right) and in the atherosclerotic vessel (left).

In SLE, several additional risk factors closely related to inflammation and autoimmunity (several autoantibodies and their respective autoantigens) have been identified as possible factors in development and progress of atherosclerosis namely; oxidized low density lipoprotein (LDL) and anti-oxidized LDL, beta 2-glycoprotein 1 [β2GP1 and anti-β2GP1], heat shock(hsp) protein and anti-hsp autoantibody systems [24]. Recently, antibodies to both apolipoprotein A-1(Apo-A-1) and to high density lipoprotein (HDL) itself, have been identified and have also been found to cross-react with anticardiolipin. As these lipoproteins are increasingly considered to be protective against atherosclerosis, the presence of such antibodies may contribute to the accelerated atherosclerosis observed in SLE and antiphospholipid syndrome [21].

These effects of chronic inflammation and immune dysregulation seen in autoimmune diseases have been found to be associated with endothelial activation and endothelial dysfunction (ED).

4. Endothelial Dysfunction (ED)—a central determinant in autoimmune disease states and atherosclerosis

Endothelial dysfunction is a key event in atherogenesis appearing long before the formation of a structural atherosclerotic lesion [22]. ED is common in most inflammatory states [23]. Chronically raised levels of inflammatory mediators may drive the inflammation that subsequently contributes to endothelial damage (Fig. 2).

Chronic ED and vascular inflammation induced both by conventional risk factors and systemic inflammation are important mechanisms in atherogenesis [22].

Chronic inflammation and ED play key roles in all stages of the atherosclerotic process. Under the influence of CVS risk factors, including inflammation, the endothelium expresses adhesion molecules (intercellular adhesion molecule 1[ICAM-1], vascular cell adhesion molecule 1 [VCAM-1], selectins) that promote the adherence of monocytes. The expression of adhesion molecules is induced by pro-inflammatory mediators-tumour necrosis alpha (TNF-α), interleukin 1 (IL-1), C-reactive protein (CRP) and CD40/CD40 ligand interaction [22,23]. The aforementioned mediators are all abundant in autoimmune diseases such as RA and exert deleterious effects on the endothelium (Fig. 2).

In systemic autoimmune diseases, like RA and SLE, endothelial dysfunction has been shown to occur [23,24]. Recent studies have demonstrated impaired endothelial function in RA patients even at the early stage of the disease, in young–middle-aged patients without CVS risk factors [25]. Similar results were also reported in SLE, indicating that inflammation per se may impair vascular function [24]. ED in SLE is also aided by immune-complex deposition, local complement

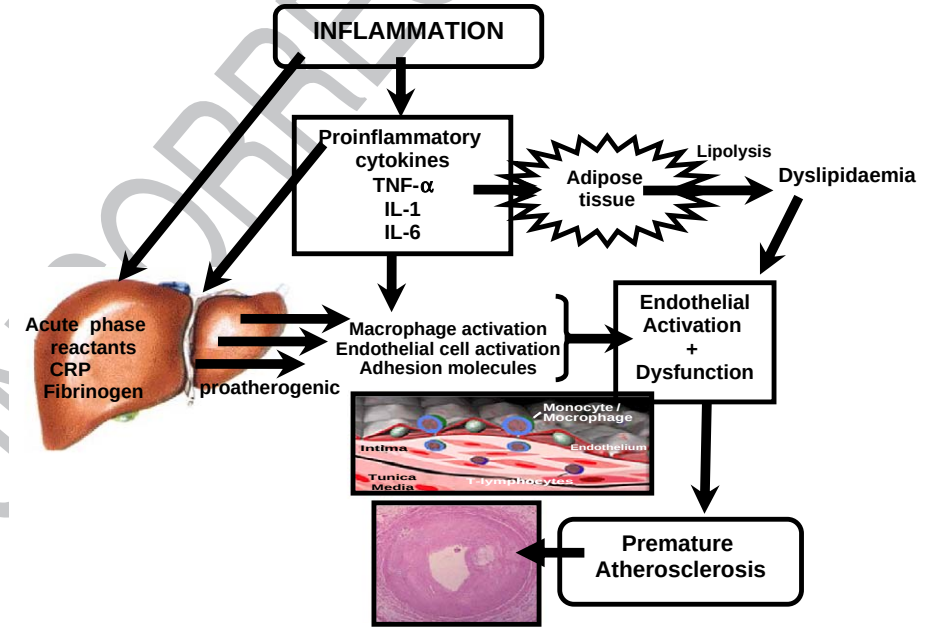

Fig. 2. Inflammation may promote atherogenesis in several ways. TNF-α = tumour necrosis factor, IL-1 = interleukin-1, IL-6 = interleukin-6, CRP = C-reactive protein.

activation and anti-endothelial antibodies. The anti-endothelial antibodies have been shown in the sera of SLE patients and seem to be related to disease activity [26]. These observations suggest that chronic inflammation may lead to ED, subsequent atherosclerosis and CVS events in autoimmune diseases like RA and SLE.

Furthermore, in both RA and SLE, disease duration and disease activity are associated with accelerated atherosclerosis. Thus, the more severe the inflammation, the more severe the atherosclerotic process. This was demonstrated in several studies where the prevalence and severity of coronary calcification was increased in patients with established RA, having longer disease duration and increased erythrocyte sedimentation rate (ESR) [27]. In yet another study it was shown that excess cardiac mortality occurred predominantly in RA patients with other extra-articular manifestations and was accompanied by persistent elevation of acute phase reactants [28]. The extent of inflammation in RA has been linked to an increased risk of CVS mortality. Investigators have shown that the number of swollen joints, independent of traditional CVS risk factors, is predictive of CVS-related deaths among Pima Indians with RA that is, more severe inflammatory activity is associated with more severe atherogenesis [29].

All this and more evidence support the notion that inflammation plays a pivotal role in vascular dysfunction explaining, at least in part, the excess morbidity and mortality observed in RA and SLE.

5. C-Reactive Protein (CRP): a mediator and marker of inflammation and cardiovascular risk

Systemic inflammation may be regarded as accelerating the atherosclerotic process. Systemic levels of inflammatory mediators such as CRP have been associated with CVS risk in the general population. Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future CVS events, the most reliable, surpassing all inflammatory and lipid markers in predicting CVS events, currently being, high-sensitivity CRP (hsCRP) [30]. Epidemiological studies have established that CRP level is an independent risk factor for myocardial infarction and stroke in men with and without risk factors [31].

CRP, an acute phase protein commonly measured in inflammatory autoimmune diseases, is now known not to be an innocent bystander, but an active and direct participant in atherogenesis, both in the early initiation of atherosclerotic lesions and in the conversion of stable to unstable plaques. The biological effect of CRP on atherosclerosis development seems to encompass a complex network of interactions with other players in immunity and inflammation, such as the complement system as well as a direct effect of CRP on the cells involved in lesion growth and development.

Recently, studies have shown that CRP possesses proatherogenic properties (Fig. 2)—it activates the complement system, induces endothelial production of monocyte chemotactic protein-1(MCP-1) and secretion of endothelin-1 (ET1) and interleukin 6 (IL-6), upregulates adhesion molecules (ICAM-1, VCAM-1, selectins), mediates macrophage uptake of LDL and stimulates monocyte production of tissue factor [32,33].

High sensitivity CRP, a means of detecting and quantifying variations in CRP, has assumed an increasingly prominent role in the detection of vascular inflammation and CVS risk [34]. Prospective epidemiological studies have shown that increased levels of CRP, predicts coronary events in healthy individuals and in patients with stable and or unstable angina [35]. This strong predictive value of CRP may be explained by its long-term stability during storage, its long-life, its lack of diurnal variation, and its lack of age and sex dependency [35].

Hand in hand with the advances in the understanding of the pathogenesis of atherosclerosis coupled with all the evidence that has come to surface and the parallels and shared pathobiology existing between the autoimmune diseases and atherosclerosis comes the better understanding and advances in the therapeutic strategies in managing the two entities.

6. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (Statins): immunomodulatory and anti-inflammatory effects

HMG-CoA reductase inhibitors, originally designed to decrease cholesterol levels have demonstrated encouraging results in lowering CVS morbidity and mortality rates in the general population and in high risk populations [36]. Accumulating evidence suggests that statins, other than lowering cholesterol levels, also influence multiple steps in the inflammatory process, including leucocyte migration and adhesion, T cell activation, nitric oxide (NO) bioavailability, generation of free radicals and angiogenesis [37]. There is substantial evidence that statins may modulate immune responses, including effects on intimal recruitment, differentiation, proliferation and secretory activity of a number of immune cells, particularly monocytes/macrophages and T cells [37].

Thus, although operating in part through lipid modulation, recent studies demonstrate broader properties

for statins, particularly in altering inflammatory pathways [38]. There is considerable interest in the use of statins in disease states associated with high-grade inflammation. In a recent double-blind randomized placebo-controlled trial it was shown that statins may provide anti-inflammatory benefit in RA [39]. Recently, we conducted a study to evaluate markers of inflammation and atherogenesis in RA patients with and without coronary artery disease (CAD) at baseline and after 9 months of atorvastatin therapy. The data showed that after 9 months of therapy, hsCRP, ESR, fibrinogen levels and the disease activity score, DAS28 score, were significantly reduced in both RA patients with and without CAD. In addition, we found a significant positive correlation between hsCRP and the DAS28 score and a significant negative correlation between hsCRP and HDL [40].

7. Conclusions

The increased prevalence of cardiovascular mortality in RA and other autoimmune diseases cannot be merely explained by the presence of traditional atherosclerotic risk factors. Inflammation plays a pivotal role in atherosclerosis. The premature atherosclerosis may be a consequence of the chronic inflammation that is part and parcel of autoimmune diseases like RA and SLE. Increases in CRP have been shown to predict future CVS events in the general population. Thus, one explanation for the excess CVS mortality observed in RA patients is that the inflammatory disease burden may lead to accelerated atherogenesis in these patients. In light of the growing evidence of increased CVS morbidity and mortality, treatment strategies in autoimmune diseases like RA should not only aim at relieving symptoms and preventing structural damage, but should also have a beneficial effect on the vasculature to reduce cardiovascular events. Risk factor modulation with agents such as statins may provide clinical benefit in the context of uncontrolled systemic inflammatory parameters. CVS reduction should be considered in the control of disease activity in patients with RA and SLE.

Take-home messages

- Inflammation, in combination with other non-traditional and traditional risk factors, contributes to cardiovascular disease in autoimmune diseases.
- Systemic inflammation confers additional risk for cardiovascular death among patients with autoimmune diseases such as RA.
- Chronic systemic autoimmune inflammatory disorders such as RA may be considered as a possible risk marker of CAD; hence, dampening of the inflammatory activity may have a favourable impact on prognosis.
- Early risk factor intervention and effective control of systemic inflammation, the major driver for excess vascular comorbidity in diseases like RA, should be incorporated into the management of systemic autoimmune diseases with the goal of protecting patients against accelerated atherosclerosis.
- Therapeutic aims in autoimmune and cardiovascular diseases should thus, converge to develop agents that modify both immune and inflammatory disease.

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