

Review

Systemic lupus erythematosus: a model for atherogenesis?

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Young women with systemic lupus erythematosus (SLE) have strikingly high rates of coronary heart disease [1–4]. Before we can solve the mystery of why these young women are so afflicted, we must first explore our understanding of cardiovascular disease in the general population. Only by coupling our knowledge of the pathogenesis of SLE and atherosclerosis and examining the risk factors common to both diseases can we begin to unravel the complexity of why these disease processes are so frequently linked.

Epidemiology of cardiovascular disease in women

A great misperception is that death from cardiovascular disease is not a major health threat for women. On the contrary, cardiovascular disease, particularly coronary heart disease and stroke, is the leading killer of women in America. In recent years, it has accounted for nearly half of all deaths in women, more than all forms of cancer combined [5]. Significant ethnic differences exist in cardiovascular disease mortality, which is 31% higher in Black than in White females [5]. Cardiovascular disease is also one of the leading causes of disability in women [6]. Estimates of disability in women survivors with coronary heart disease and stroke aged 55–64 yr approximate 36% and 62%, respectively [7]. Previous reports suggest that women incur more than half the costs (estimated to be \$274 billion in 1998) of cardiovascular disease, including lost productivity from disability [5].

Although coronary heart disease is the leading cause of death among women, coronary events are uncommon before the age of 55 yr [8]. Women lag 10–20 yr behind men in the incidence of myocardial infarction, but this female advantage diminishes with age [8, 9]. Although most of the classic risk factors for coronary heart disease in men are also found in women, the magnitude of their effects may be different [9, 10]. The most dramatic example is diabetes mellitus, which is a stronger risk factor for coronary heart disease in women than in men and is the most common cause of premature coronary heart disease in women [11]. Other conditions that

lessen the female advantage include familial hypercholesterolaemia [12] and premature menopause [13].

Less publicized entities associated with premature coronary heart disease are rheumatoid arthritis [14–16] and SLE [1–4]. It has been well proven that women with SLE are at significant risk of premature cardiovascular disease, now one of the leading causes of death in this population.

Potential risk factors for cardiovascular disease in SLE

Classical risk factors for cardiovascular disease in SLE appear to be similar to those in the general population: hypercholesterolaemia, diabetes mellitus, smoking, obesity, hypertension, and sedentary lifestyle [1, 2, 17]. In a recently reported study, the incidence of myocardial infarction and stroke in SLE were significantly increased, even after controlling for expected events based on known population-based risk models, suggesting that the diagnosis of SLE or its treatment is the strongest known risk factor for cardiovascular disease [18].

Treatment with corticosteroids has been implicated as a risk factor for atherosclerosis [2, 19, 20]. Whether corticosteroids are directly atherogenic or whether they are causally related to atherosclerosis through enhancement of cardiovascular disease risk factors such as hyperlipidaemia, hyperglycaemia, hypertension, or obesity remains unclear [21]. In addition, corticosteroids may be a proxy for severe disease, since patients with severe lupus are more likely to be treated with higher doses of corticosteroids for longer periods of time.

Renal disease, seen in up to 50% of SLE patients, may be a risk factor for atherosclerosis. Endothelial cell damage produced by immune complexes, or other mediators of inflammation, may be responsible for activation of the coagulation system in patients with lupus nephritis, resulting in elevated plasma and urine levels of fibrinogen, a precursor of fibrin. Plasma fibrinogen levels have been reported to be higher in non-lupus postmenopausal women than in both premenopausal women and women taking oestrogen therapy [22]. Elevated fibrinogen levels have been linked to the risk of future heart disease in women [23]. Increased fibrinogen, along with the abnormal lipid profiles and hypertension frequently seen in patients with nephritis,

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may result in an increased risk of cardiovascular disease in lupus.

Parallels between the pathogenesis of SLE and atherosclerosis

Chronic inflammation

It is currently believed that atherosclerosis in the general population results from a combination of numerous risk factors. In addition to traditional risk factors, inflammatory processes are now suspected to be important in atherogenesis [24]. In particular, the inflammatory processes associated with vascular injury are thought to mediate the development of atherosclerotic lesions. Epidemiological observations have linked inflammation with cardiovascular events. C-reactive protein, an acute phase reactant, was shown to predict independently the risk of future myocardial infarction and stroke in men with otherwise favourable risk factor profiles [25], people with multiple risk factors [26], and people with unstable angina [27].

Inflammatory processes probably contribute to atherogenesis in SLE, a disease characterized by chronic inflammation. This author's hypothesis is that the pathogenesis of cardiovascular disease in lupus is multifactorial, due to an interaction between traditional cardiovascular risk factors and inflammation-induced and antiphospholipid antibody-mediated vascular injury/thrombosis from the underlying disease. Corticosteroid treatment and renal disease with resulting hypertension may accelerate the atherosclerotic process in lupus. Furthermore, the immune dysregulation characteristic of SLE probably plays an important role in atherogenesis.

Endothelial cell injury

In the 'response to injury' hypothesis of atherosclerosis, several different sources of injury to the endothelium can lead to endothelial cell dysfunction [28], including immune complexes, viruses, and other toxins such as homocysteine, all of which are also relevant to SLE (Fig. 1). Such injury results in increased permeability and adhesiveness of the endothelium, procoagulative properties, and vasoactive molecule expression [24]. A prolonged inflammatory response with inadequate down-regulation is characteristic of SLE and may actually be an important facilitator of atherogenesis in these patients.

Entrapment and subsequent oxidation of low density lipoprotein (LDL) at the site of endothelial injury is an important step in the formation of an atherosclerotic plaque. Endothelial cell adhesion molecules, whose expression is up-regulated, bind and recruit monocytes/macrophages and T lymphocytes to the site of injury. The inflammatory cells then migrate and localize sub-endothelially. The macrophages ingest oxidized LDL (oxLDL) and, in conjunction with T cells and smooth muscle cells, form the 'fatty streak', which can then progress to a fibrous plaque. Rupture of the plaque and

formation of a thrombus result in a clinical ischaemic event.

Immune complexes. In SLE, immune complexes that fix C1q may be a source of arterial injury initiating atherogenesis. These complexes bind to C1q receptors on the endothelium, triggering an up-regulation of adhesion molecules such as E-selectin and intercellular and vascular cell adhesion molecules 1 (ICAM-1 and VCAM-1) on the endothelial surface [29]. These C1q fixing immune complexes have also been shown to down-regulate sterol 27-hydroxylase, leading to increased accumulation of cholesterol in the endothelium [30]. Increased amounts of immunoglobulins, complement components, and C5b-9 complexes have been reported in atherosclerotic lesions [31–33]. One hypothesis of atherogenesis is that this intense immune/inflammatory reaction in the plaque may precipitate plaque ulceration, rupture and thrombosis [34], a process that may be accentuated in SLE.

CD40–CD40L interactions. CD40 is a molecule expressed on a variety of cells including B lymphocytes, macrophages, fibroblasts, and endothelial cells. Activated T cells transiently express CD40 ligand (CD40L). In SLE, the interaction between CD40L on T cells and CD40 on B cells is involved in the production of pathogenic autoantibodies [35, 36]. Under normal circumstances the immune system allows only transient expression of CD40L. However, patients with SLE express abnormally high levels of CD40L on both T and B cells and the overall number of CD40L-positive cells is increased [35]. Furthermore, in lupus nephritis patients, CD40 expression is up-regulated on endothelial cells.

The binding of CD40L to CD40 on endothelial cells results in increased expression of VCAM-1, ICAM-1, and E-selectin [37], adhesion molecules important in facilitating vascular inflammation both in SLE and in atherosclerosis. Furthermore, CD40L induces the release of interleukin-1 by vascular cells, potentially enhancing the inflammatory response [38]. In genetically modified mice with hypercholesterolaemia that are deficient in apolipoprotein E, ICAM-1 is increased at lesion-prone sites [39]. Inhibition of CD40 with blocking antibodies reduced lesion formation in these mice [40]. Thus, increased CD40–CD40L interactions may have implications in both the pathogenesis of SLE and the premature atherosclerosis seen in this population.

Autoantibodies. Antiphospholipid antibodies provide additional evidence for immune-mediated atherogenesis. The most common association of antiphospholipid antibodies in SLE is with venous and arterial thromboembolic events, stroke, and recurrent fetal loss [41]. Elevated levels of antibodies to cardiolipin, a phospholipid, have been associated with myocardial infarction in non-lupus patients [42, 43] and with macroangiopathy in diabetics [44]. Antibodies to cardiolipin may recognize several different antigenic structures; some antibodies bind the lipid component and others bind β_2 -glycoprotein I or prothrombin [45, 46]. Interestingly, there is evidence that some anticardiolipin antibodies

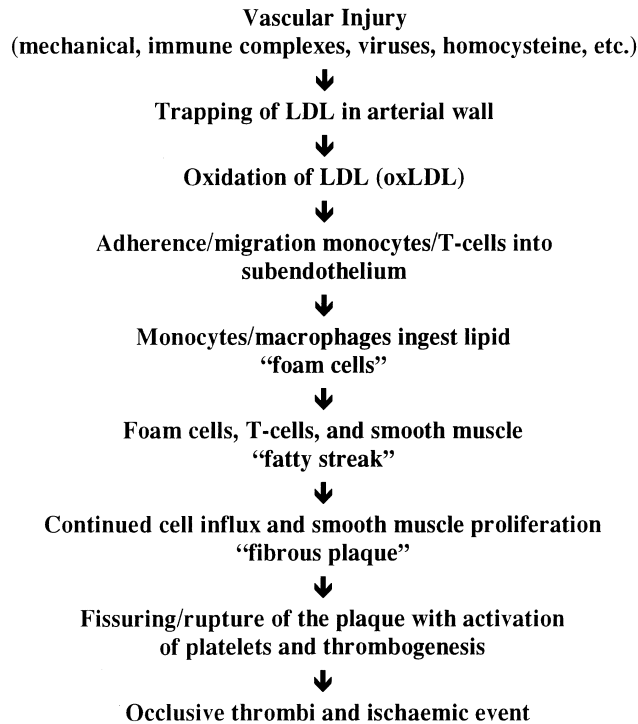
“RESPONSE TO INJURY” MODEL OF ATHEROGENESIS

FIG. 1. Injury to the vascular endothelium is one of the earliest changes that occurs in atherogenesis. Sources of such injury can be mechanical in nature or arise from immune-mediated processes, viral infection, or toxins such as homocysteine. The resultant endothelial dysfunction leads to altered permeability of the endothelium, increased affinity for leucocytes and platelets, production of vasoactive molecules, and induction of procoagulant properties. In SLE, C1q-fixing immune complexes may be a source of injury to the endothelium, resulting in expression of cell adhesion molecules (ICAM-1, VCAM-1). Interactions between CD40 on endothelial cells and CD40L can stimulate expression of ICAM-1, VCAM-1, and E-selectin. LDL particles are also a major source of injury to the endothelium. When LDL particles are trapped in the arterial wall they become progressively oxidized and can be internalized by macrophages, resulting in the formation of foam cells. Antibodies to oxLDL may actually facilitate foam cell formation. The inflammatory response also stimulates the migration and proliferation of smooth muscle cells that together with T cells and foam cells form the fatty streak. Continued cell influx and smooth muscle proliferation leads to formation of the fibrous plaque. As the fibrous plaque grows, it may protrude into the arterial lumen and impede blood flow, or may rupture or fissure resulting in occlusive thrombosis, ultimately leading to the ischaemic event. (Adapted from [28].)

may be directed against cross-reactive epitopes common with oxLDL. The presence of antibodies binding to oxLDL is considered a marker of atherosclerosis [47] and has been reported to be predictive of future myocardial infarction [43, 48].

Several investigators have demonstrated that antibodies to oxLDL were higher in SLE patients than control subjects and correlated with anticardiolipin antibody levels [49, 50]. The recognition of oxLDL by anticardiolipin antibodies may be partially explained by several observations. Anticardiolipin antibodies of the anti- β_2 -glycoprotein I type may recognize oxLDL in complex with β_2 -glycoprotein I [51]. Binding of antibodies to β_2 -glycoprotein I-oxLDL complexes may increase LDL uptake into macrophages via Fc receptors, promoting the formation of the fatty streak (Fig. 1). Furthermore, some antiphospholipid antibodies have been shown to be directed against oxidized phospholipids [52].

The significance of these related observations is not completely understood, but one could speculate that

these oxidative processes result in the generation of a common antigenic epitope recognized by both antibodies to phospholipid and oxLDL. In support of this theory is the observation that lysophosphatidylcholine (LPC) is a major factor in the antigenicity of oxLDL [53] and has been found in atherosclerotic plaques [54]. It was recently reported that patients with SLE had elevated levels of antibodies to both oxLDL and LPC [55]. LPC can also be generated enzymatically by phospholipase A2 hydrolysis of phosphatidylcholine, a major phospholipid component of cellular membranes. This is of particular relevance in SLE where elevated levels of phospholipase A2 expression and activity have been documented [56]. In this case both oxidation of LDL and hydrolysis of phospholipid result in a common product of known antigenicity.

Apolipoprotein A1 (apo A1), the major protein component of high-density lipoprotein (HDL) that acts as an acceptor of cholesterol from peripheral blood monocytes, is important in the prevention of atherosclerosis

[57]. A high prevalence of antibodies to apo A1 has also been documented in the sera of patients with SLE [58]. It is possible that antibodies to apo A1 may impede the uptake of cholesterol into HDL, although this remains to be determined.

Infectious agents. A role for infectious agents has been proposed in the pathogenesis of atherosclerosis [59, 60]. In the 'response to injury' model, infectious agents may serve as a cause of vascular injury or may potentiate injury by stimulating an inflammatory response. Two organisms currently considered likely candidates in atherogenesis are *Chlamydia pneumoniae* and cytomegalovirus (CMV). Many studies have documented a serological association between *C. pneumoniae* infection and the development of atherosclerosis [61, 62]. High CMV antibody levels were reported in patients requiring cardiovascular surgery [63], and in the Atherosclerosis Risk in Communities (ARIC) study CMV seropositivity was reported to be correlated with asymptomatic carotid artery wall thickening [64]. Furthermore, pathological and microbiological evidence has confirmed the presence and viability of *C. pneumoniae* and CMV in atherosclerotic plaques [65]. *In vitro* studies demonstrated that infection of endothelial cells with CMV resulted in divergent patterns of E-selectin, ICAM-1, and VCAM-1 expression [66] and promoted endothelial procoagulant properties [67].

Although the evidence is circumstantial, infectious agents have gained increasing attention as potential contributors to the development of SLE. They may initiate or flare SLE by disturbing immunoregulation, causing tissue damage leading to the release of autoantigens, or by eliciting a specific immune response by molecular mimicry. Of particular interest are the Epstein-Barr virus [68, 69] and herpes zoster [70]. Although viral infection has not been examined in association with atherosclerosis in lupus, it is interesting to speculate that viral factors may play a role in the premature atherosclerosis seen in this population.

Other sources of endothelial injury. Another source of potential vascular injury in lupus is elevated homocysteine levels. Homocysteine may have both direct and indirect injurious effects on the endothelium [71, 72]. It is prothrombotic, increases collagen production, and decreases the availability of nitric oxide [73-75]. Both the Physicians' Health Study and the Framingham Heart Study reported an association between homocysteine and an increased relative risk of coronary artery disease, stroke, and carotid vascular disease [76, 77]. Homocysteine was elevated in one population of lupus patients and was associated with arterial thrombosis [78]. The reasons for hyperhomocysteinaemia in SLE are unclear, and may include dietary- and/or treatment-related factors.

Summary

We must redirect our focus on the aetiology of cardiovascular disease in SLE to include non-traditional risk factors such as immune and inflammatory mediators.

From an epidemiological standpoint, the relationship between these immunological and inflammatory markers and disease can be examined, but more sensitive methods of defining cardiovascular disease will be required. Relying on clinical events alone often results in an underestimation of the true prevalence of vascular disease since atherosclerosis may be present for many years before a clinical event occurs. Furthermore, epidemiological studies relying on clinical events as outcomes are difficult since the absolute number of cardiovascular events in SLE is very low. With the advent of sensitive non-invasive screening techniques, such as B-mode ultrasound and electron beam computed tomography (CT), we are now better equipped to measure subclinical vascular disease and associated risk factors.

From a basic science perspective, we should concentrate on the common pathways in the pathogenesis of SLE and atherosclerosis. This effort will involve clarifying the role of CD40-CD40L interactions and antibodies directed against phospholipids and cholesterol-carrying lipoproteins such as LDL and HDL, as well as pursuing common infectious triggers.

When considering strategies for prevention of premature cardiovascular disease in SLE, modifying traditional risk factors will be only a part of the future programmes. It seems likely that the strongest predictors of cardiovascular disease in this population will be immune and inflammatory in nature. I propose that better biological therapies for SLE such as anti-CD40 ligand antibodies will have a greater impact on prevention of atherosclerosis than altering traditional risk factors alone. This concept is supported by findings in post-cardiac transplant vasculopathy. Accelerated coronary atherosclerosis is the leading cause of mortality in cardiac transplant recipients who survive beyond the first year of transplantation [79, 80]. Although the exact pathogenesis of cardiac allograft vasculopathy is not completely understood, considerable evidence suggests that it is an immune-mediated disease that is different from the cell-mediated rejection commonly seen post-transplant [79, 80]. The proliferative disease is limited to the allograft arterial and venous tree, the nature of the allograft vascular involvement is often diffuse, and development of the disease occurs in allografts of animal models with some histocompatibility mismatch but not in isografts. Furthermore, there is evidence to suggest that more aggressive immunosuppressive treatment directed at blocking cellular processes common to the immune response and vascular lesion formation may be effective in reducing or preventing cardiac allograft vasculopathy [81]. One could hypothesize that treatment directed towards specific immune dysregulation in SLE that does not have the unfavourable side-effect profile of agents such as corticosteroids will be beneficial in preventing premature atherosclerosis in this population.

In response to Elizabeth Barrett Conner's eloquent discussion in her 1995 Ancel Keys Lecture on 'why women are so superior with regard to coronary heart disease?' [82], one should be quick to acknowledge that like women with diabetes mellitus, women with SLE

nearly erase the female advantage. Given the inflammatory and autoimmune nature of SLE and the associated premature development of atherosclerosis, this unique population may provide an interesting model to examine further the process of atherogenesis.

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