Inflammation-mediated rheumatic diseases and atherosclerosis

For over 20 years, premature coronary heart disease has been recognised as a major determinant of morbidity and mortality in patients with systemic lupus erythematosus (SLE).1-4 Less appreciated is the fact that the same holds true for patients with rheumatoid arthritis (RA).5,6 These two autoimmune diseases share a propensity to target women of childbearing age and a treatment armamentarium that includes corticosteroids and other immunosuppressive agents. Despite clear distinctions in pathophysiology, the immune dysfunction unique to each disease results in a chronic inflammatory state, which may have implications for the atherogenesis seen in these young patients. As we compare and contrast potential cardiovascular risk factors in these two autoimmune diseases, we may further our understanding of why these young women are at high risk for premature atherosclerosis.

Epidemiology of cardiovascular disease in SLE and RA
Women with SLE have a high incidence of coronary heart disease.1-4 Several investigators have convincingly shown that women with SLE under the age of 45 are at substantially increased risk of ischaemic heart disease.1-4 We reported that women with SLE aged 35–44 were over 50 times more likely to have a myocardial infarction than were women of similar age from a population based sample (rate ratio = 52.43, 95% CI 21.6 to 98.5).7 In contrast, women with SLE in the 45–64 year age group were only two to four times more likely to have a myocardial infarction than women without SLE of the same age. We also found a small decline in the incidence rates for myocardial infarction in women with SLE aged 45–64 compared with those having the same diagnosis aged 35–44. The reasons for this are unclear. A difference in overall survival is an unlikely explanation as mortality rates from all causes were not significantly different between women in these two age strata. A plausible hypothesis may be the prothrombotic effects of oestrogen in combination with the generally more common renal disease and associated hypertension in the younger women, and a relatively protective effect of declining oestrogen levels in women aged 45–54. Similarly, Ward reported that women with SLE aged 18–44 were 2.27 (95% CI 1.08 to 3.46) times more likely to be admitted to hospital with an acute myocardial infarction than young women without the disease.8 This increased risk of admission to hospital with ischaemic heart disease for women with SLE compared with women without the disease diminished substantially with increasing age. Whether vasculopathy is more common in younger women with SLE owing to age related differences in clinical manifestations of SLE is uncertain. Nevertheless, it is clear that young women with SLE who should be otherwise protected from ischaemic heart disease are at the highest risk.

Deaths due to coronary artery disease have been reported in several RA mortality series. Standard mortality ratios (SMRs) for patients with RA dying from circulatory diseases have ranged from 1.13 to 5.25,9-11 though a recent inception cohort from the Netherlands showed no increased mortality at 10 year follow up.12 Such discrepancies may reflect differences in genetic susceptibility to atherosclerosis, dietary practices, variations in RA treatment, and duration of follow up. The most striking findings of increased mortality in RA due to coronary heart disease have been in young women aged 15–49, where SMRs are as high as 3.64.13 Studies in RA analysing the sexes separately show significant differences in relative risk of death due to myocardial infarction and congestive heart failure in men and women, with women having a higher risk than men (SMR 1.68 v 1.41).14 Two prospective studies have shown the morbidity and mortality of cardiovascular disease in RA. Mutru et al reported an increase in mortality from cardiac diseases (p<0.008), primarily due to cardiac failure, in a Finnish RA cohort compared with matched controls over 10 years; the observed increase was much more striking in men than women.15 Furthermore, in a second study, the incidence of myocardial infarction and congestive heart failure in a population based cohort of 450 patients with RA was 50% higher than in controls matched for age and sex.16 Seropositive patients had nearly double the risk of controls. Although sex related risk is inconsistent across studies, factors that might account for such contradictions are practices in postmenopausal hormone replacement and variations in smoking, exercise, and health care maintenance between the sexes.

These data substantiate the observation that young women with SLE and RA are developing atherosclerotic heart disease at higher rates than expected.

Potential risk factors for cardiovascular disease in SLE and RA
Identifying relevant risk factors is more difficult than proving that cardiovascular disease is a major health concern for patients with SLE and RA. Classical risk factors for cardiovascular disease in the general population also
appear to be important in SLE. These include hypercho-
esterolaemia, diabetes mellitus, smoking, obesity, hyper-
tension, and sedentary lifestyle. Other risk factors implicated in cardiovascular events in SLE include ever use or longer use of corticosteroids and older age at SLE diagnosis. In addition, evidence suggests that having SLE is an independent risk factor for cardiovascular disease. In a recent study the incidence of stroke and myocardial infarction in SLE was estimated after control-
ing for expected events based on known population based risk models. After adjustment for the effect of known classical risk factors, the risks of myocardial infarction and stroke were significantly increased, suggesting that the diagnosis of SLE or its treatment is the strongest known risk factor for cardiovascular disease. In our studies we found that having SLE was independently associated with the presence of carotid plaque measured by duplex ultrasound (unpublished data). We compared 158 normo-
tensive, non-diabetic women with SLE who had no previous cardiovascular or cerebral event with 99 healthy women of similar age, sex, and menopausal status. Forty six of the 158 women with SLE and 16 of the 99 healthy women had plaque (29% vs 16%, p=0.02). In a logistic regression model, adjusting for age and blood pressure, women with lupus were more likely to have plaque (odds ratio (OR) 2.37, 95% CI 1.1 to 5.09, p=0.03). The 106 premenopausal women with lupus had a higher prevalence of plaque than 73 premenopausal healthy women (20% vs 8%, p=0.03). After adjusting for age and blood pressure, premenopausal women with SLE were more likely to have plaque (OR 3.71, 95% CI 1.36 to 10.16, p=0.01). In con-
trast with the premenopausal women, there was no significant difference in carotid plaque prevalence be-
tween the women with postmenopausal SLE and healthy women. Thus we found that after adjusting for traditional cardiovascular risk factors, having SLE was independently associated with the presence of carotid plaque in premenopausal women. These findings suggest that char-
acteristics unique to lupus render patients, particularly younger women, at extremely high risk for cardiovascular disease.

Studies examining the prevalence and relative contribu-
tion of traditional cardiovascular risk factors in the development of atherosclerotic heart disease in RA have not been as extensive as in SLE. Wallberg-Jonsson et al reported that diabetes mellitus, corticosteroids, disease modifying agents, or hormone replacement therapy had no influence on risk of death or first cardiovascular event in a group of patients with RA. Few investigators have exam-
ined whether clinical features of RA influence the develop-
ment of cardiovascular events. Gabriel et al showed that risk ratios for myocardial infarction or congestive heart failure in seropositive cases were higher (RR = 1.93; 95% CI 1.37 to 2.71) than in all patients with RA combined (RR = 1.48; 95% CI 1.11 to 1.98). To our knowledge the association between the presence of rheumatoid nodules, bony erosions, or inflammatory markers and cardiovascular disease in RA has not been examined. As with SLE, it will be difficult to distinguish the relation between cardio-
vascular disease and RA disease severity and treatment, as surrogates for disease severity often include more aggres-
sive treatment.

Potential features of SLE that may facilitate the athero-
sclerotic process include corticosteroid use, renal disease with resulting hypertension, and the presence of antiphos-
pholipid antibodies. Treatment with corticosteroids has been implicated as a risk factor for atherosclerosis either owing to direct atherogenic effects or causally related to atherothrombosis through enhancement of traditional cardio-
vascular disease risk factors such as hyperlipidaemia, hyperglycaemia, hypertension, or obesity. Cumulative cor-
"tico" corticosteroid doses tend to be higher in patients with SLE than in those with RA. Despite these differences, cortico-
steroids probably have a role in the atherosclerosis seen in both these rheumatic diseases.

The risk of atherosclerosis increases in otherwise healthy postmenopausal women, in part owing to the drop in endogenous oestrogen levels. However, in both SLE and RA the abnormalities in sex hormone levels tend towards higher oestrogen or lower androgen levels, or both. In women with active lupus, reduced levels of androgens (androstenedione, dehydroepiandrosterone (DHEA), de-
hydroepiandrosterone sulphate (DHEAS), and testosterone) have been found. In addition, both male and female patients with SLE have been found to have abnor-
malities in oestrogen metabolism. Several studies have reported increased levels of 16-hydroxylated oestrogen metabolites as well as lower testosterone levels, resulting in a relative “hyperoestrogenic” state. Evidence suggests that women with RA have lower DHEA and DHEAS levels than normal women and those with osteoarthritis. A similar pattern was noted in young premenopausal women who later developed RA, suggesting that a relative hypo-
androgen state is present before disease onset. Hence in both SLE and RA, if any inherent abnormalities of the sex hormone milieu exist, one might predict that such alterations would confer protection against atherosclerosis rather than increased susceptibility. This protective effect, however, may be offset by the prothrombotic effects of oes-
trogens, particularly in the presence of antiphospholipid antibodies, which are common in SLE.

Another potential disease or treatment related risk fac-
tor in SLE and RA is raised serum homocysteine, which may have both direct and indirect injurious effects on the endothelium. Both the Physicians’ Health Study and the Framingham Heart Study reported an association be-
tween homocysteine and an increased risk of coronary artery disease, stroke, and carotid vascular disease. Treatment with methotrexate, the most commonly prescribed disease modifying antirheumatic drug in the United States, raises plasma homocysteine levels in patients with RA through its anti-folate effects. This is attenuated by folate administration. However, patients with RA, both with and without methotrexate treatment, have been reported to have raised homocysteine levels. Raised homocysteine levels have also been noted in one group of patients with SLE and were associated with arte-
rial thrombosis. The reasons for hyperhomocysteinaemia in SLE are not clear but may include factors related to diet and treatment.

**Links between chronic inflammatory diseases and atherogenesis**

There are interesting parallels between the pathogenesis of SLE, RA, and atherosclerosis. Although many factors cause atherosclerosis, inflammation at the site of vascular injury probably mediates atherogenesis. It is, therefore, not surprising that atherosclerosis develops in SLE and RA, autoimmune diseases characterised by chronic inflam-
mation. In fact, molecular and cellular mediators of inflammation in SLE and RA may be key to the development of atherosclerotic lesions. Although vasculitis is a feature of both SLE and RA, necropsies have failed to provide evidence of active coronary arteritis, carditis, or valvular heart disease as a common cause of death. Thus the vascular inflamma-
tion linked with atherosclerosis in these groups is most probably subclinical and not associated with overt vasculitis.
Epidemiological observations have linked inflammation with cardiovascular events. C reactive protein, an acute phase reactant often raised in active autoimmune disease, was shown to predict independently the risk of future myocardial infarction and stroke. Persistent vascular injury may result in a prolonged low level acute phase response with a decrease in serum albumin level, and an increase in globulin and haemostatic proteins, including fibrinogen. Fibrinogen is a precursor to fibrin, an essential element for blood clotting. Raised fibrinogen levels have been linked to a risk of future heart disease in women. Thus inflammation may have some procoagulant and atherosclerosis-inducing effects. The anti-inflammatory and antiplatelet effects of salicylates and non-steroidal anti-inflammatory drugs may play a part in the primary prevention of atherosclerotic vascular disease in RA, and perhaps in SLE where these agents may be used less regularly. It is unknown whether the deleterious effects of corticosteroids offset the benefits of these agents.

Both cellular and humoral components of the immune system probably contribute to atherosclerosis in SLE and RA. In SLE, immune complexes that fix C1q may be a source of arterial injury initiating atherogenesis. These complexes bind to receptors on the endothelium, triggering an upregulation of adhesion molecules such as E-selectin and intercellular and vascular cell adhesion molecules 1 (ICAM-1 and VCAM-1) on the endothelial surface. Adhesion molecules bind and recruit monocytes/macrophages and T cells to migrate into the subendothelium where, in conjunction with oxidised low density lipoprotein (oxLDL), they form the fatty streak. In the absence of downregulation of this inflammatory process, the fatty streak develops into a fibrous plaque that can rupture and lead to an ischaemic event. These adhesion molecules were associated with both incident coronary heart disease and carotid atherosclerosis in the Atherosclerosis Risk in Communities study, independent of other known risk factors. C1q fixing immune complexes have also been shown to downregulate sterol 27-hydroxylase, leading to increased expression and activity has been reported in SLE. Although CD40L is only transiently expressed under normal circumstances, its expression is raised in patients with SLE. Furthermore, in patients with lupus nephritis, CD40 expression is upregulated on endothelial cells. Important to our discussion of atherogenesis is the fact that endothelial cells can be stimulated to express VCAM-1, ICAM-1, and E-selectin by CD40L positive T cells. In a genetically modified murine model with hypercholesterolaemia, blocking antibodies to CD40 reduced atherosclerotic lesion formation. Thus CD40-CD40L interactions may have implications in the pathogenesis of both SLE and atherosclerosis.

The similarities between the inflammatory and immunological mechanisms playing a part in atherogenesis and RA were highlighted in a recent editorial by Pasceri et al. Enzymes involved in collagen degradation, which are released by activated inflammatory cells (macrophages and mast cells) in atherosclerotic plaques, are probably important in destabilisation of plaques. Collagen degradation is also relevant in the pathogenesis of RA. Similarly, recent studies have shown that neoangiogenesis, an important factor in the pathogenesis of RA, may also contribute to formation of atherosclerotic plaque. Other components of the immune system considered integral to rheumatoid synovitis may also be important in the development of atherosclerosis. Specifically, CD4+ T cells and proinflammatory cytokines TNFα, IL1 ( interleukin 1), and IL6 ( interleukin 6) promote atherosclerotic lesions and also are considered key factors in the promotion of RA joint disease. TNFα, IL1, and IL6 upregulate adhesion molecules, important in the migration of inflammatory cells to rheumatoid synovium. Specifically, ICAM-1 and E-selectin are expressed on RA synovial endothelium and mediate transmigration of T cells in inflamed synovium, an essential step in the development of rheumatoid pannus. As described above, these adhesion molecules have a role in recruiting T cells and monocytes/macrophages to the site of vascular injury, a key step in formation of the atherosclerotic plaque. Furthermore, TNFα may represent a class of biologically active molecules that are responsible for the development and progression of heart failure.

Antiphospholipid antibodies provide additional evidence for immune mediated atherogenesis. Venous and arterial thromboembolic events, stroke, and recurrent fetal loss represent the most common association of antiphospholipid antibodies in SLE. In patients without lupus and in diabetic patients with macroangiopathy increases in anticardiolipin antibodies have been associated with myocardial infarction.

Antiphospholipid antibodies recognise epitopes in protein-phospholipid complexes. These epitopes may include anionic phospholipids, such as cardiolipin, proteins binding plasma phospholipid, such as β2 glycoprotein I and prothrombin, or new epitopes resulting from the protein-phospholipid complex. Evidence also suggests that many antiphospholipid antibodies recognise the oxidised state of the phospholipid either alone or in complex formation with protein. Lysophosphatidylcholine (LPC) can be generated enzymatically from the hydrolysis of phosphatidylycerine, a major phospholipid component of cellular membranes, by phospholipase A2, an enzyme whose raised expression and activity has been reported in SLE. LPC is also formed during the oxidation of LDL. It is a major factor in the antigenicity of oxLDL, and has been found in atherosclerotic plaque. Thus the oxidation of LDL and the hydrolysis of phospholipid result in a common antigenic product, LPC. It was recently reported that patients with SLE had raised levels of antibodies to both oxLDL and LPC. Interestingly, there is evidence that some cardiolipin antibodies may be directed against cross reactive epitopes common to oxLDL and LPC. Several investigators have reported raised levels of antibodies to oxLDL in patients with SLE and that these levels correlated with cardiolipin antibody levels. Thus there may be a common antigenic site recognised by anticardiolipin, antioxLDL, and antiLPC antibodies that may be related to the oxidised state of these molecules. There is also evidence that some cardiolipin antibodies that recognise oxLDL may be of the anti-β2 glycoprotein I type and recognise oxLDL in complex with β2 glycoprotein I.

Antibodies to oxLDL are considered markers of atherosclerosis and have been reported to predict future myocardial infarction. Uptake of LDL into macrophages through Fc receptors, and the subsequent formation of the fatty streak, may be enhanced by the binding of antibodies to β2 glycoprotein I-oxLDL complexes.
In summary, antibodies to oxLDL, LPC, and cardiolipin may all recognise a common oxidative product of known antigenicity. It is unclear what part these related antibodies play in the atherothrombosis seen in patients with SLE.

Conclusions

Although the pathophysiological mechanisms of SLE and RA are distinct and disease specific, the resulting increased expression of cellular adhesion molecules, the recruitment of inflammatory cells, and the lack of appropriate downregulation of these proinflammatory processes may be the major link between these autoimmune diseases and atherosclerosis. Other factors common to both diseases may that facilitate this process include corticosteroid use, raised homocysteine levels, hormonal factors, and traditional cardiovascular risk factors. However, the relative importance of these specific risk factors in atherogenesis in these diseases is not known. It is interesting to speculate what the effect might be of more aggressive pharmacological treatment and improved management of SLE and RA on the cardiovascular disease so often found in these patients. On the one hand, the expected improvement in longevity may make cardiovascular disease an even greater concern. However, it is our belief that more widespread use of biological treatments, such as antibodies to CD40L in SLE and TNFα antagonists in RA, may reduce cardiovascular events by more effectively controlling the inflammatory process, as well as reducing corticosteroid requirements. Of interest, TNFα antagonists, which are currently being used in the treatment of RA, are presently under study in the treatment of heart failure. We, therefore, suggest that future prevention strategies for premature cardiovascular disease in SLE and RA must not only include modification of traditional risk factors, but also must consider and explore anti-inflammatory, immune-modulatory, metabolic, and hormonal interventions.
A 75 year old white man was referred to the clinic for assessment of left foot pain.

At the age of 16, while in India, he had contracted leprosy and subsequently had developed ulcers over the midtarsal area of his right foot, leading eventually to a right below-knee amputation at the age of 44. He had also had amputation through the distal aspects of most of his fingers and had undergone removal of the toes of his left foot. When seen in the clinic he had localised ulceration and cellulitis of the left foot. When seen in the clinic he had localised ulceration and cellulitis of the left foot.


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