Risk factors for coronary heart disease in connective tissue diseases

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***Abstract*:** Atherosclerosis and cardiovascular disease risk is enhanced in certain connective tissue diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic vasculitis and antiphospholipid syndrome. The reason for this accelerated process is likely to be multifactorial. Traditional risk factors are more prevalent in some of these patient groups compared with the general population (e.g. smoking in RA and hypertension in SLE). However, these factors do not fully explain that enhanced risk. Chronic inflammation associated with these disorders as well as some specific autoantibodies have been shown to contribute to this increased risk although their role remains controversial. The role of therapies is unclear and while steroids may exacerbate metabolic risk factors, the anti-inflammatory effects of traditional and more novel biological therapies may reduce overall cardiovascular risk in these populations. We recommend proactive screening for modifiable cardiovascular risk factors in patients with these conditions.

***Keywords*:** atherosclerosis, cardiovascular disease, connective tissue disease, risk factors

Introduction

Premature coronary heart disease is a leading cause for morbidity and mortality in patients with connective tissue diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic vasculitis. The excess risk is most notable in those of a younger age and in SLE especially, the excess risk may be up to 50-fold that of a general population sample [Manzi *et al.* 1997]. Both clinical atherosclerotic events and subclinical atherosclerosis have been studied in a number of conditions, although it is clear that SLE and RA have been the most comprehensively studied in this regard [Haque *et al.* 2008; El-Magadmi *et al.* 2004; Roman *et al.* 2003]. The aim of this review is to highlight the current state of knowledge as to the risk of clinical and subclinical atherosclerotic disease across the range of connective tissue diseases and how comprehensive our knowledge is according to diagnostic subgroup. We will also focus on some of the similarities and differences between conditions in regard to atherosclerotic risk and the factors that may drive this.

SLE and cardiovascular disease

Although better use of treatments has resulted in improved long-term survival in SLE patients with SLE still experience increased morbidity and mortality due to cardiovascular disease (CVD) [Manzi *et al.* 1997]. Manzi and colleagues reported that overall, women with SLE have a 5–6-fold increased risk of CVD and women with SLE aged 35–44 years had more than 50 times increased risk for CVD [Manzi *et al.* 1997]. Postmortem studies also have described a significant burden of atherosclerosis in more than 50% of deceased patients regardless of the cause of death [Abu-Shakra *et al.* 1995].

There are certain factors that are associated with the future development of CVD in the general population. Many of these factors were derived from the large community-based studies such as the Framingham study. These classic risk factors are broadly divided into irreversible factors such as age, gender and family history and modifiable factors including raised cholesterol, hypertension, diabetes and smoking [Bruce, 2005].

Several case–control studies indicated that classic coronary heart disease (CHD) risk factors are associated with the development of atherosclerotic disease in SLE. Two factors have been described in a number of studies namely, hypercholesterolaemia and older age at diagnosis of

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SLE [Svenungsson *et al.* 2001; Manzi *et al.* 1997; Gladman and Urowitz, 1987]. Of note is that hypertension and diabetes are both significantly more common in SLE patients compared with healthy controls [Bruce *et al.* 2003]. Regarding the impact of risk factors to future CHD risk, Bruce and colleagues also found that in an inception cohort of SLE patients with persistent hypercholesterolaemia followed up for a mean of 12 years, 24% developed a new CVD event compared with only 3% of those with normal cholesterol levels [Bruce *et al.* 1999]. In addition, other factors also have been identified such as longer disease duration, diabetes, hypertension and smoking [Frostegard, 2005; Bruce *et al.* 2003; Manzi *et al.* 1997].

A prospective cohort study by Esdaile and colleagues however, found that patients with SLE have a 7.5–17-fold excess risk of CVD even after adjustment for the baseline Framingham risk estimates [Esdaile *et al.* 2001]. Therefore, although patients with SLE have a higher prevalence of traditional risk factors, these do not fully explain the excess cardiovascular morbidity and mortality that indicates the presence of other novel or disease-associated risk factors. One obvious candidate is of course steroid therapy, which is assumed to be a key mediator of CHD. Steroids at high doses can cause many metabolic abnormalities including central obesity, hypertension, glucose intolerance and alterations of lipid profiles. It would be expected that patients on steroid therapy would therefore have a higher risk of cardiovascular events since all these side effects are known risks for CHD. It was noted in 1975 by Bulkeley and colleagues that treatment with steroid for more than 1 year was associated with an increased prevalence of atherosclerosis and CHD [Bulkeley, 1975].

It has, however, been noted that low dose steroids (<10 mg daily) do not adversely affect the lipid profile in SLE but doses of >10 mg daily can cause increased low-density lipoprotein (LDL) cholesterol and triglycerides [MacGregor *et al.* 1992]. The effect of high-dose steroid was confirmed by other studies [Bruce *et al.* 1999; Keng Hong *et al.* 1994]. Conversely, Okawa-Takatsuji and colleagues reported that corticosteroid use in SLE patients with renal impairment lead to decreased lipoprotein (a) (Lp(a)) levels, which could be of benefit as the latter is considered a risk factor for developing heart disease [Okawa-Takatsuji *et al.* 1996].

Another likely risk factor is the state of chronic systemic inflammation, which is a main characteristic of the disease. This systemic inflammation is associated with the release of a number of inflammatory mediators, cytokines, chemokines and adhesion molecules [Pearson *et al.* 2003; Ridker *et al.* 2000]. These mediators are now believed to contribute to the process of atherosclerosis [Hansson, 1999, 2001]. Gabay and Kushner [1999] documented that the acute phase response was associated with altered hepatic synthesis of some coagulation proteins and lipoprotein metabolism. Thus, an inflammatory disease process itself can induce alterations in the lipid profile, which can be considered a risk factor for CVD. In lupus, a pattern of dyslipoproteinaemia was described by a number of investigators as low LDL, elevated very low-density lipoprotein (VLDL) and triglycerides and reduced high density lipoprotein (HDL) [Borba and Bonfai, 1997]. A number of other alterations in lipid profiles have also been documented namely increased oxidized phospholipids, Lp(a), small dense LDL and proinflammatory HDL. All of these additional alterations in lipids resulting from chronic inflammation may further enhance the risk for CHD in SLE.

Moreover, the autoimmune nature of the disease process is also characterized by the production of various autoantibodies, in particular antiphospholipid antibodies (APLA) and lupus anticoagulant, which are associated with thrombotic risk in SLE patients and in the general population [Frostegard, 2005]. Approximately 30–50% of SLE patients have APLA and up to half of these develop antiphospholipid syndrome [Petri, 2004]. Anti-oxLDL antibodies (a significant subfraction of APLA) were also detected in patients with CVD [Sherer *et al.* 2001]. Doria and colleagues demonstrated that the titre of these autoantibodies was higher in SLE patients and the level was correlated with increased intima-media thickness (IMT), which is a surrogate marker for atherosclerosis [Doria *et al.* 2003].

RA and CVD

RA is the most common inflammatory rheumatic disease with a prevalence of 0.5–2% worldwide [Haque *et al.* 2008]. Patients with RA have a reduced life expectancy with a standardized mortality ratio of 2.0 [Naz and Symmons, 2007]. Premature atherosclerosis has been identified as a major cause for reduced life expectancy in patients with RA. Two studies in RA patients

showed that cardiovascular events account for 40–50% of deaths [Sihvonen *et al.* 2004; Wallberg-Jonsson *et al.* 1997]. Del Rincon and colleagues reported that patients with RA have a 4-fold increase in cardiovascular events compared with controls [Del Rincon *et al.* 2001]. A recent meta-analysis showed that patients with RA have 1.63-fold higher risk for myocardial ischaemia compared with the general population [Levy, 2008]. However, since RA is much more common in the population than SLE and RA patients tend to be older, this smaller relative risk does however, translate to a much greater population burden of CHD related to RA.

There are several factors that predispose RA patients to cardiovascular risk. Smoking is more prevalent in RA populations and is indeed a risk factor for the development of RA [Symmons *et al.* 1997; Silman, 1996]. Dyslipidaemia in RA is also similar to the profile noticed in SLE with reduced HDL and LDL with elevated VLDL and triglycerides. This is most likely secondary to chronic inflammation [Georgiadis *et al.* 2006].

Systemic inflammation does appear to be a key factor in this context. It has been documented that patients with RA who are rheumatoid factor-positive have a 50% higher cardiovascular mortality than age- and sex-matched controls [Wallberg-Jonsson *et al.* 1997]. In patients with RA C-reactive protein (CRP) level at baseline was an important predictor of subsequent cardiovascular mortality, which indicates the important role of inflammation in the pathogenesis of CVD [Goodson *et al.* 2005]. Atherosclerosis appears to be correlated with disease duration in RA patients suggesting prolonged exposure to chronic inflammation predisposes to CHD burden [Del Rincon *et al.* 2007].

Interestingly, it has also been suggested that CHD risk may be increased prior to the onset of RA [Maradit-Kremers *et al.* 2005], and this may relate firstly to the excess risk associated with smoking and perhaps to low-grade inflammation prior to clinical onset of synovitis. In established disease, Del Rincon *et al.* [2005] also noted that systemic inflammation was the key risk factor in RA patients under 54 years of age. There also appears to be an additive or perhaps synergistic effect between these factors in the context of RA. Farragher and colleagues found that smoking, the presence of the shared epitope and anticyclic citrullinated peptide (anti-CCP) antibodies were all associated with increased CHD mortality RA patients [Farragher *et al.* 2008]. There was a synergistic effect in patients with all three factors. Similarly Gonzalez-Gay and colleagues documented increased cardiovascular mortality and endothelial dysfunction in association with HLA-DRB1. He also documented increased cardiovascular events in association with CRP and erythrocyte sedimentation rate [Gonzalez-Gay *et al*. 2007]. This indicates that the chronic inflammatory process centrally associated with RA can promote cardiovascular events and increase mortality in genetically predisposed patients.

Methotrexate is widely used as a mainstay treatment of RA. It has been associated with reduced cardiovascular mortality risk [Krishnan *et al.* 2004; Choi *et al.* 2002]. Indeed in a prospective study of 1240 patients with RA, methotrexate use was associated with a 60% reduction in overall mortality and a 70% reduction in cardiovascular mortality specifically [Choi *et al.* 2002]. This suggests that adequate control of inflammation in RA may be an important mechanism in reducing CHD risk. Alternatively a reduction in steroid exposure by use of better disease-modifying antirheumatic drug therapy may also contribute to this observation. Interestingly use of antitumour necrosis factor-α agents also appears to reduce CHD risk, especially in patients whose arthritis respond well to therapy [Dixon *et al*. 2007].

Systemic sclerosis and macrovascular disease

Systemic sclerosis (SSc) is an autoimmune disease which, in contrast to the inflammatory processes that predominate in SLE, is characterized by vasospasm, vascular proliferation and a profibrotic phenotype. In the microcirculation, intimal proliferation and deposition of extracellular matrix results in small-vessel obliteration and tissue anoxia. The development of accelerated atherosclerosis in SSc is however, less clear. While some studies have shown an increase in carotid IMT in SSc patients [Yaniv *et al.* 2007], this finding has not been consistent across studies [Shoenfeld *et al.* 2005]. One study described increased coronary calcification scores in SSc but whether this is attributable to atherosclerosis will need further confirmation as ectopic calcification can occur as part of the disease itself [Mok *et al.* 2009]. Clinically, there is also little evidence for increased macrovascular complications such as stroke and myocardial infarction in SSc patients.

Primary systemic vasculitis and risk of CVD

Primary systemic vasculitides (PSV) comprise a group of immune-mediated conditions that cause necrotizing inflammation of blood vessels and are characterized by systemic inflammation and a range of ischaemic complications related to occlusion and stenosis of blood vessels. In addition, haemorrhagic complications can occur as a result of small vessel disease or aneurismal dilatation and vessel rupture. PSV can be classified as small-, medium-, or large-vessel vasculitides according to the size of blood vessels involved. In addition, certain syndromes are associated with the production of antineutrophil cytoplasmic antibodies (ANCA) termed ANCA-associated vasculitides. The outcome of PSV has improved from being life threatening to a remitting–relapsing condition owing to the use of current treatment, particularly cytotoxic drugs such as cyclophosphamide [Fauci *et al.* 1978; Mukhtyar *et al.* 2009a].

There are few reports regarding cardiovascular sequelae in vasculitis. Most of the reports relate to Kawasaki disease (KD) or Henoch–Schonlein purpura. It was reported that flow-mediated dilatation (FMD), an endothelium-dependent response, was reduced in patients with KD compared with healthy controls and that this persisted for several years after the disease had settled [Dhillon *et al.* 1996]. Similarly Cheung and colleagues have reported increased carotid IMT in children with KD even without a documented coronary artery disease [Cheung *et al.* 2007]. The presence of a proatherogenic lipid profile (low HDL, high LDL) has also been reported in children with KD, which remains persistent for several years and was worse for patients with coronary sequelae [Cheung *et al.* 2004]. There was also increased arterial stiffness in these children. Patients with Takayasu's arteritis have been shown to have accelerated atherosclerosis involving the carotid arteries similar to lupus patients and significantly greater than healthy controls [Seyahi *et al.* 2006].

There are several factors of relevance to the increased cardiovascular burden in systemic vasculitides including endothelial activation and damage and different mechanisms have been implicated for these processes. Among these mechanisms are immune complex-mediated activation, ANCA-associated neutrophil–endothelial interactions, and continuous interaction between the endothelium and adhesion molecules and cytokines [Savage, 2002; John *et al.* 1989]. Systemic inflammation with sustained release of inflammatory cytokines and adhesion molecules may favour the development of atherosclerosis. A study by De Leeuw and colleagues reported increased carotid artery IMT in patients with systemic vasculitis (Wegener's granulomatosis) compared with control subjects [De Leeuw *et al.* 2005]. In this study there was no difference in traditional factors in the two groups, however, there was an excess of inflammatory markers (i.e. hsCRP, metalloproteinases) in patients compared with controls. This suggests that excess inflammation and vascular remodelling might contribute to the development of atherosclerosis. This inflammatory process can be aggravated by the accumulation of oxidized LDL, which was reported in some vasculitic conditions together with the production of anti-oxLDL antibodies [Örem *et al.* 2002].

In addition to the chronic inflammatory state in PSV, most patients are treated with high-dose and long-term corticosteroid therapy for at least 2 years, which may of course also contribute to the risk for CVD [Mukhtyar *et al.* 2009b,c].

Primary antiphospholipid syndrome

Primary antiphospholipid syndrome (PAPS) is a prothrombotic condition characterized by recurrent arterial/venous thrombosis and pregnancy morbidity with persistent presence of elevated antiphospholipid antibodies. These antibodies may induce a proinflammatory state and hence contribute to the prothrombotic state [Belizna *et al.* 2007]. PAPS is defined by an arterial thrombotic manifestation in a proportion of patients, although it has generally been argued that this is primarily a thrombotic problem. More recently it has been noted that patients with PAPS have higher carotid IMT compared with controls [Jara *et al.* 2006]. In addition, they have also been noted to have increased arterial stiffness and more carotid plaques than a control population [Belizna *et al.* 2008].

Others have also noted that immunoglobulin G anticardiolipin titres independently predict carotid IMT in patients with PAPS [Ames *et al.* 2002]. The traditional risk factors therefore do not appear to be the only factors responsible for accelerated atherosclerosis. The presence of autoantibodies such as anti-oxLDL and anti-beta-2-glycoprotein-I (βGPI) also contributes to accelerated atherosclerosis by several

mechanisms [Belizna *et al.* 2008]. It is likely therefore that within this family of autoantibodies certain subgroups will be found to be proatherogenic. For example, anti-βGPI has been shown to accelerate the uptake of oxidized LDL into monocyte/macrophages via an Fc receptor-dependent mechanism [Matsuura *et al.* 2002].

Cardiovascular risk in Sjögren's syndrome

Sjögren's syndrome is an autoimmune disease characterized by the production of autoantibodies and cellular infiltration of the exocrine tissues. Unlike other connective tissue diseases, primary cardiovascular involvement is rare in this condition. Studies examining clinical CHD and the presence of CHD risk factors in Sjögren's syndrome are limited. A few case reports describe the occurrence of stroke, which were attributed to vasculitis rather than accelerated atherosclerosis [Bragoni *et al.* 1994]. One case report documented a sudden death of a young female patient who had Sjögren's syndrome. The cause of death was ischaemic heart disease induced by arteriosclerosis, which it was proposed to be due to Sjögren's syndrome [Inoue *et al.* 2008]. There has been no formal study confirming an increased CHD risk in Sjögren's syndrome. Lodde *et al.* [2006] investigated serum lipid levels in Sjögren's syndrome. They found significant difference in mean HDL and total cholesterol between patients and controls. This derangement was associated with serological markers of inflammation. Whether this translates to increased cardiovascular consequences however, requires further study.

Adult inflammatory myositis

Polymyositis and dermatomyositis are immune-mediated conditions that primarily affect skeletal muscle and usually require high doses of corticosteroids over a prolonged period to control the condition. In addition inflammatory myocarditis is a recognized complication in a subgroup of patients [White *et al.* 1988]. The epidemiological studies regarding the association between these conditions and CVD are rare. A study by Tisseverasinghe and colleagues [2009] indicated an increased incidence of arterial events in patients with inflammatory myopathies and this was predicted by high blood pressure and lipid disorders. Given the profound and chronic inflammatory state as well as the need for high-dose immunosuppression, further examination of patients with inflammatory myopathies is of great interest to confirm or refute whether CHD occurs at increased frequency in these conditions.

Undifferentiated connective tissue disease

Undifferentiated connective tissue disease refers to patients who have clinical and serological manifestations of autoimmune diseases but have insufficient features to be classified as having a specific connective tissue disease syndrome. These conditions are characterized by a milder, albeit chronic inflammatory, clinical profile without major organ involvement. Crucially they also require less intense immunosuppressive therapy such as steroids [Mosca *et al.* 2008]. A recent study by Mosca and colleagues demonstrated impaired endothelium-dependent and -independent vasodilatation in the microcirculation of the forearm [Mosca *et al.* 2009]. This suggests that even in the absence of traditional risk factors and corticosteroid therapy, the chronic inflammation associated with autoimmune diseases can impair both nitric oxide-dependent and endothelium-independent vasodilatation in the microcirculation. The clinical consequences of this require further study.

Summary

Connective tissue diseases are generally characterized by chronic inflammation and also the requirement for immunosuppressive therapy such as corticosteroids. An increased association between these conditions and clinical CVD has been noted and is particularly strong in patients with SLE. From a population impact however, the small but significant association between RA and CHD is more relevant. The 'substrate' for accelerated atherosclerosis in the context of these conditions is likely to be primarily driven by the inflammatory vascular damage that characterizes their pathogenesis. Endothelial dysfunction has been demonstrated in a number of these conditions and is thought to be the initial step in atherogenesis. Many conventional risk factors for atherosclerosis are also altered in these conditions, for example, increased hypertension and diabetes in SLE and a higher prevalence of smoking in RA. Table 1 summarizes the main traditional and disease-associated risk factors in these conditions. Other changes, such as increased oxidized LDL, have also been noted in a number of these disorders. Treatment with corticosteroids in particular can exacerbate classic risk factor profiles and may also contribute to endothelial dysfunction. Finally, a number of the autoantibodies that these patients have may also be markers

Table 1. Clinical and subclinical cardiovascular associations of selected connective tissue diseases.

Connective tissue disease syndrome	Clinical cardiovascular disease associated	Subclinical atherosclerosis	Classic risk factors	Disease-related factors	Therapy
Systemic lupus erythematosus	↑ × 5–6 CHD ↑ × 8–10 stroke	↑ Carotid plaque ↑ Aortic PWV ↓ FMD ↑ Carotid calcification	↑ Cholesterol Older age Hypertension	Complement activation IFN Antiphospholipid antibodies/lupus anticoagulant	Steroids ↑ risk Antimalarials ↓ risk
Rheumatoid arthritis	↑ × 1.5 CHD	↑ Carotid plaque ↑ Aortic PWV ↓ FMD	Smoking Hypertension	Anticyclic citrullinated peptide antibodies Shared epitopes Rheumatoid factor C-reactive protein	Methotrexate ↓ risk Antitumour necrosis factor ↑ FMD Anti-tumour necrosis factor ↓ MI
Primary systemic vasculitides	↑ CHD	↑ Carotid plaque	↔	Systemic inflammation Antineutrophil cytoplasmic antibodies?	Steroid↔?
Sjögren's syndrome	—	—	—	—	—
Systemic sclerosis	↔	↑ Carotid IMT	↔	—	
Primary antiphospholipid syndrome	↑ MI ↑ stroke	↑ Carotid IMT	↔	Antiphospholipid antibodies	—
Adult myositis	MI and stroke	—	Hypertension Lipid abnormalities	—	—

CHD, coronary heart disease; FMD, flow-mediated dilatation; IFN, type 1 interferon; IMT, intima mediated thickness; MI, myocardial infarction; PWV, pulse wave velocity.

of risk, for example, anti-CCP in RA and APLA in SLE and PAPS. Certain antibodies may also directly influence the atherogenic process.

From a clinical standpoint we recommend screening for cardiovascular risk factors in these populations. For example, we view SLE as a CHD equivalent condition. With this in mind, the target is strict control of traditional risk factors including modifying lifestyle, treating cholesterol and blood pressure to strict targets and supporting the patient towards smoking cessation and weight reduction [Wajed *et al*. 2004]. We also suggest using other steroid-sparing agents and, where possible, introducing antimalarials to reduce overall steroid exposure over time.

Therefore, clinicians managing these conditions should be alert to the cardiovascular risk associated with these conditions and screen and manage patients accordingly. Further research is needed however, to examine some of these syndromes in more detail to understand better the differences and similarities between the inflammatory state and therapy exposures that may explain some of the differences noted so far. Understanding these differences will improve our understanding of the inter-relationship between chronic inflammation and atherogenesis.

Conflicts of Interest Statement

Professor Bruce has received honoraria and/or research income from Abbott Pharmaceuticals, Wyeth, Hoffmann-La Roche, Bristol Myer Squibb and UCB. Dr Al-Husain has no conflicts to declare.

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