Atherosclerosis in systemic lupus erythematosus

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Abstract

Cardiovascular disease (CVD), comprising coronary heart disease and stroke, is one of the most important causes of death in patients with systemic lupus erythematosus (SLE). The risks of developing both clinical CVD and sub-clinical atherosclerosis are increased in patients with SLE. This increase is not fully explained by traditional cardiovascular risk factors such as smoking, hypertension and elevated cholesterol, and it is believed that immune dysfunction also contributes to CVD risk in SLE. In particular, recent studies have shown that abnormalities in both serum lipid profile and the autoantibody and T lymphocyte response to lipids may play a role in development of atherosclerosis.

The standard CVD risk calculation algorithms based on traditional risk factors underestimate the risk of developing CVD in patients with SLE. Thus, novel algorithms incorporating new biomarkers such as pro-inflammatory high-density lipoprotein and use of imaging techniques such as carotid ultrasound scanning may become increasingly valuable.

Keywords: Systemic lupus erythematosus; Cardiovascular disease; Atherosclerosis; Lipids; Risk stratification; Autoantibodies; Invariant natural killer T cells

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease with a prevalence of 97 per 100,000 people in the United Kingdom [1]. It presents most commonly in young women, with a female to male ratio of 9 to 1 [1]. Cardiovascular disease (CVD) due to atherosclerosis is currently recognised as one of the leading causes of death among patients with SLE [2,3], with approximately a quarter of all deaths in a large multinational study of almost 10,000 patients with SLE being due to CVD [2]. In the general population, CVD risk is dominated by traditional risk factors such as male sex, increasing age, diabetes, smoking, hypertension and elevated low-density lipoprotein (LDL) cholesterol [4–6]. However, for SLE, the early onset of atherosclerosis in this ordinarily low-risk population of predominantly younger women [7] cannot be explained fully by those traditional factors. It has therefore been proposed that the atherosclerotic process is possibly accelerated [8–10] in patients with SLE due to a complex interplay of traditional and lupus-specific risk factors [4,11,12]. Here we aim to review the clinical and epidemiological evidence regarding atherosclerosis and CVD in the context of SLE and address some of the proposed contributory mechanisms relating to lipids and the immune response to lipids. We also discuss emerging biomarkers that may allow for better CVD risk stratification in patients with SLE and the imaging methods that may offer an accurate assessment of the actual atherosclerotic burden of individual patients.

Epidemiological and clinical evidence for the increased risk of CVD in patients with SLE

SLE is one of the strongest known risk factors for CVD [10,11,13]. The range of cardiovascular involvement in SLE is broad including atherosclerosis, vascular inflammation/vasculitis, Raynaud's phenomenon, endothelial dysfunction and a pro-coagulant tendency associated with the presence of antiphospholipid antibodies. Focusing on atherosclerosis-related CVD, Magder and Petri reported a 2.66-fold increased risk of CVD in the Hopkins Lupus Cohort compared with the Framingham controls [14]. The impact of CVD-related events on both mortality and morbidity is tremendous: the incidence of coronary artery disease both in its acute (MI) and chronic (angina and chronic heart failure) forms is over 7 times greater in patients with SLE than in healthy controls, even after accounting for traditional CVD risk factors, including sex, age and lipid profile [7,11]. In particular, younger female patients with SLE (age 35–44 years) have an over 50 times greater risk of having a MI compared with the Framingham dataset [7]. When considering the typical bimodal mortality pattern found in SLE, the real importance of CVD becomes apparent: a decade after the diagnosis of SLE, one of the leading causes of death is MI [2,15]. Patients with SLE also have a greater risk for stroke, with an overall prevalence that can reach 20%, and high recurrence rate and greater mortality than matched controls [16,17].

Furthermore, the prevalence of sub-clinical atherosclerosis is also considerably high in patients with SLE. Studies in multiple units, using different imaging techniques such as vascular ultrasound [9,18,19] and electron beam tomography [8], have consistently shown that patients with SLE have significantly higher prevalence of atherosclerotic plaque than healthy controls.

The reason why SLE is such a dramatic risk factor for atherosclerosis and CVD is yet to be fully explained. Decisive evidence associating specific lupus-related factors to the development of atherosclerosis has been proved difficult to obtain, perhaps because even in very large cohort studies, the actual number of patients with CVD events is small. For example, in a large multi-centre study of the Systemic Lupus International Collaborative Clinics (SLICC) inception cohort, Urowitz *et al.* found that among 1249 patients followed for a mean of 8 years, there were 31 atherosclerotic events [20]. In univariate analysis, all the factors significantly associated with increased risk of atherosclerosis were generic rather than SLE-specific. These included male gender, increased age, smoking, hypertension and family history of CVD, but in multi-variable analysis, only non-modifiable risk factors, namely age and male gender, remained significant [20].

On the one hand, the presence of longstanding systemic inflammation associated with persistently active SLE could contribute to plaque formation and disruption. On the other hand, it has been found that patients with lupus have a high prevalence of traditional CVD risk factors such as hypertension, altered lipid profile and impaired glucose tolerance [4,6,11], which to some extent may be the result of chronic treatment with corticosteroids [21,22]. However, to date, no undisputed correlation has been found between corticosteroid use and atherosclerosis in SLE. Magder and Petri reported that the risk of cardiovascular events is increased by 2- to 5-fold for daily prednisolone doses above 10 and 20 mg, respectively [14]. This could be due to the effects of corticosteroids on blood pressure and lipid profile, as reported for the Hopkins Lupus Cohort, where a daily dose of 10 mg of prednisolone was associated with an average total cholesterol rise of 0.19 mmol/L, a weight gain of 5.5 lbs and an increased BP by 1.1 mmHg [23]. However, there are also conflicting data suggesting that there is an increased CVD risk among patients who are under treated with steroids, which could imply that poorer disease control is more relevant in determining a higher CVD risk than steroid treatment *per se* [8].

In summary, the raised CVD risk is likely due to an interplay between direct vascular damage arising from inflammatory phenomena associated with SLE, such as vasculitis and immune-complex-mediated endothelial cell damage; treatment-related factors, such as steroid-induced hyperlipidaemia, hypertension and obesity; and other SLE-independent factors, such as homocysteine levels, smoking and family history [10]. Contributing factors indirectly related to SLE, namely nephrotic syndrome secondary to lupus nephritis and the presence of anti-phospholipid antibodies (aPL), should also be considered [21,24]. Although the majority of SLE study groups report an association between CVD-related morbidity and mortality, and anti-

phospholipid antibody positivity [14,25], there are other studies where this association was not found to be significant [26]. In addition, Farzaneh-Far *et al.* found that the presence of aPL antibodies in patients with SLE was associated with mitral valve disease but not with myocardial, carotid or coronary abnormalities [19].

Treatment can also affect CVD-risk in a positive way: the use of hydroxychloroquine, for example, may play a potentially protective role as it has been shown to be associated with lower cholesterol levels, independently of other variables [27], and may potentially counteract the negative effects of prednisolone on lipid profile [27]. Furthermore, hydroxychloroquine appears to inhibit platelet aggregation and decrease the binding of anti-β_2GP1 to phospholipid layers, thus decreasing the risk of thrombosis [28–30].

Cardiovascular risk stratification in patients with SLE

Regardless of the vascular territory predominantly affected by atherosclerosis, identifying asymptomatic patients with already significant sub-clinical disease is the key for primary prevention of symptomatic CVD. It was based on this premise that risk stratification algorithms have repeatedly been developed and improved in a bid to calculate the future risk of cardiovascular events with the highest predictive value possible. For the general population, the main risk stratification tools are based on levels of well-established CVD risk factors such as age, sex, serum cholesterol, smoking and blood pressure. The Framingham risk score [31] is the most widely used, but others have also been developed, for example, the Reynolds score [32], which includes high-sensitivity C Reactive Protein~~RP~~ (hsCRP) and the Sheffield table system [33]. These different methods are similar in their overall low sensitivity and specificity for development of CVD as they exclude various emerging, genetic and otherwise unknown risk factors. Moreover, the vast majority of these indices fail to take into account the presence of autoimmune diseases that have been shown to influence CVD risk such as SLE or rheumatoid arthritis (RA). An exception is the QRISK algorithm, which takes into account the diagnosis of RA as one of its risk factors for life-long CVD [34].

In the context of SLE, none of these CVD risk prediction algorithms are ideal. For example, because the Framingham risk score is heavily weighted for age and male gender, the risk of coronary artery disease in young women with SLE is greatly underestimated [12,35]. The inability to assess accurately the actual CVD risk for each individual patient has led to an inability to shift CVD-associated mortality and morbidity in SLE, opposing the trend observed for other causes of mortality such as lupus nephritis [2,36]. There is a need for alternative ways to assess and identify patients with SLE with potentially higher risk for developing CVD, which could include both blood tests and non-invasive scanning aimed at detecting sub-clinical atherosclerosis.

Ahmad *et al.* published a study focusing on assessing the strength of the association between traditional cardiovascular risk factors and presence of carotid plaque assessed by B-mode ultrasound [37]. The ultrasound findings of 200 women with SLE were compared with those of 100 healthy controls. An increased prevalence of plaque was observed among the SLE cohort, particularly in the internal carotid artery (11% vs 4%; $P < 0.05$). Traditional risk factor models performed less well in SLE compared with controls, but when using a multivariable model, which included SLE-related factors (including azathioprine use and aPL), a significant performance improvement was noted.

The use of SLE-specific stratification algorithms has been proposed, with particular emphasis on composite risk-assessment scores including both traditional risk factors and novel biomarkers. A good example is the PREDICTS score proposed by McMahon *et al.* who argue that this is a useful tool to improve the identification of patients with SLE, who have a greater risk for CVD [38]. This study included 210 patients with SLE and 100 age-matched healthy control subjects who underwent 2D carotid ultrasound to assess the presence of atherosclerotic plaque and the intima-media thickness (IMT) at two time points (0 and 2 years). For all the participants, complete data on traditional CVD risk factors (age, sex, diabetes, hypertension and lipid profile) and treatment were collected (including cumulative steroid use). Moreover, all the participants were tested for a panel of serological variables that included pro-inflammatory HDL (piHDL), leptin, serum TNF-like weak inducer of apoptosis (sTWEAK), serum homocysteine, hsCRP, adiponectin and apolipoprotein A1. Although some variables were shown to correlate significantly with the presence of plaque, namely the presence of diabetes, age 48 years or above, high piHDL, high leptin and high sTWEAK levels, no single variable demonstrated an ideal combination of sensitivity and specificity. Consequently, a high-risk PREDICTS profile was proposed on the basis of the presence of at least three positive biomarkers or a combination of diabetes plus at least one of the biomarkers considered. From this definition, patients who had the high risk profile had a 28-fold increased risk of the presence of plaque and increased IMT progression, with a 79% specificity and 89% sensitivity (negative predictive value 89% and positive predictive value 64%) [38].

Currently, however, SLE-specific CVD risk algorithms are not in widespread use, but clinicians must nevertheless do their best to manage the traditional risk factors because although they do not contribute the whole CVD risk in SLE, they contribute some of it. There is an evidence base for strategies to manage these traditional factors [39]. SLE subjects should be screened annually for cardiac risk factors—one report showed that only 26% of patients had four cardiac risk factors assessed annually [40]. In the SLICC cohort, hypercholesterolaemia was not treated in up to two-thirds of patients.

Management of CVD risk can be undertaken by a target-based approach. As SLE is a very high-risk condition for CVD, some experts have suggested that it can be viewed as a ‘coronary heart disease equivalent’ such as diabetes, and therefore, targets for hypertension and raised cholesterol should be adjusted accordingly [41].

Abnormal lipids and increased atherosclerosis in SLE

Lipids are known to play a key role in the development of atherosclerotic plaques, with LDL and high-density lipoprotein (HDL) cholesterol being measured routinely in clinical laboratories and used in assessment of CVD risk. As noted above, however, LDL levels are of limited value in the assessment of CVD risk in patients with SLE [35]. Some authors have reported increased very-low-density lipoprotein (VLDL) and triglycerides but reduced HDL in patients with SLE [42,43], arguing that this profile promotes the oxidation of LDL and the development of atherosclerosis. Oxidative modifications of LDL including β_2-glycoprotein 1-oxidised LDL complexes have been identified in patients with SLE and are associated with arterial thrombosis [44]; moreover, altered lipid profile has also been shown to influence non-CVD related outcomes, particularly regarding adverse renal outcomes [45].

The pathogenesis of the altered lipid profile observed in SLE is not yet fully established, but it is believed to be multifactorial. The presence of sustained inflammation most likely plays a central role, namely through the increase in inflammatory cytokines such as tumour necrosis factor α (TNF α) and interleukin 6 (IL-6), which have been shown to influence lipid levels, shifting them towards an atherogenic profile [46,47].

HDL metabolism is increasingly recognised as a likely pivotal step in the development of atherosclerosis in SLE. The functional unity of HDL relies on structural and enzymatic integrity, which are dependent to a great extent on apolipoprotein A1 (ApoA1) and paraoxonase (PON), respectively [48].

A mechanism that could contribute to the increased CVD risk in SLE is the presence of dysfunctional HDL (d-HDL)—also known as piHDL. In general, total HDL levels correlate inversely with the risk of atherosclerosis-related events [49]. However, when reviewing the data from the Framingham cohort, over 40% of events occurred in subjects with normal HDL levels [50] and subsequent studies have shown that a ‘normal’ lipid profile does not necessarily exclude the risk of CVD as a significant number of events occur in subjects with normal HDL and LDL [51,52]. This led to the hypothesis that there could be a dysfunctional form of HDL with compromised anti-inflammatory activity (i.e. inability or decreased ability to prevent oxidation of LDL). Van Lenten *et al.* described a series of experiments through which the function of HDL was hindered in the presence of an acute phase-like environment and hypothesized that this could be due to the displacement and/or exchange of proteins associated with HDL, namely PON and ApoA1 [53]. Undurti *et al.* explored the impact of MPO-induced modifications on HDL function and showed not only that, through MPO-catalysed oxidation, there was a loss of non-cholesterol efflux actions of HDL, namely of its anti-apoptotic and anti-inflammatory effects, but also that the modified HDL particles actually had a pro-inflammatory action, namely enhanced NF-κB activation and increased expression of vascular surface adhesion molecules [54]. It has been suggested that d-HDL levels correlate better with the presence of CVD than total HDL levels [51]. The fact that inflammation appears to be a key factor in determining the shift from ‘normal’ HDL to d-HDL led to the exploration of its potential role in chronic inflammatory conditions such as SLE and RA. McMahon *et al.* assessed d-HDL levels in 154 women with SLE and reported that those patients had significantly higher levels of d-HDL than both healthy controls and patients with RA, and this difference was further enhanced in patients with SLE who also presented with CVD [55,56]. The presence of d-HDL also appears to correlate with *in vivo* hallmarks of atherosclerosis (i.e. presence of plaque or thickened IMT). McMahon *et al.* reported that d-HDL was detected in a greater proportion of patients with plaque compared with those without plaque and that the presence of d-HDL was also associated with thicker IMT, even in patients with no prior

diagnosis of CVD, and proposed that d-HDL could potentially be used to identify patients with increased atherosclerotic risk [56].

Immune response to lipid and development of atherosclerosis in SLE

Both the humoral and T cell response to lipids may be abnormal in patients with SLE, potentially contributing to the development of atherosclerosis.

Given that SLE is characterised by the presence of several autoantibodies, the hypothesis that components of the HDL particle could be targeted by the immune system has been proposed, and the presence of anti-ApoA1 and anti-HDL in the sera of patients with SLE has been reported by different research groups [48,57–59]. The atheroprotective role of ApoA1 is well established, and there is evidence to support that presence of anti-ApoA1 may contribute to the development of atherosclerosis in non-SLE patients, namely in patients with acute coronary syndromes, RA and diabetes [60–62]. Furthermore, Montecucco *et al.* have shown that the presence of anti-ApoA1 IgG is associated with increased intra-plaque macrophage neutrophil and metalloproteinase content and inversely with collagen *in vivo* [63]. This profile has been shown to be associated with increased plaque vulnerability and increased risk of plaque rupture, suggesting that the presence of anti-ApoA1 IgG may be associated with high-risk plaques [63]. However, although our group at University College London has demonstrated that levels of anti-ApoA1 vary with disease activity in patients with SLE, we have not shown any association with CVD so far [58,59].

Invariant natural killer T cells (*i*NKT cells) are a small population of specialised immune cells, comprising <1% of peripheral blood mononuclear cells in humans. Uniquely amongst T cells, they respond exclusively to lipid antigens presented by the CD1d molecule on antigen presenting cells [64]. Upon stimulation with lipid antigen, *i*NKT cells react very rapidly by proliferating and releasing a wide range of either pro- or anti-inflammatory cytokines that can go on to *trans*-activate other immune cells. Thus, *i*NKT cells have an immunomodulatory function. Studies in mice show that *i*NKT cells are involved in both autoimmunity and atherogenesis [65], and we and other researchers have previously identified reduced *i*NKT cell frequency and defective *i*NKT cell function in patients with active SLE [66]. In a recent paper, we compared the number and phenotype of *i*NKT cells in patients with SLE who either had or did not have carotid/femoral plaque on ultrasound scanning [67]. Intriguingly, we found that the group with plaque had more *i*NKT cells and that these cells adopted an anti-atherogenic phenotype and could polarise macrophages into an anti-inflammatory, anti-atherogenic M2 phenotype [67]. These *i*NKT cell properties were lost in patients who had moved from sub-clinical atherosclerosis to clinical CVD. These findings support an atheroprotective role for *i*NKT cells driven by serum lipids and incorporating an effect on monocyte polarisation. This protective role is not present in the absence of plaque and is triggered during the early stages of atherosclerosis but is lost or overwhelmed during the development of clinical atherosclerosis [67].

Use of vascular imaging to assess atherosclerotic burden in patients with SLE

Many different imaging techniques have been used to investigate the cardiovascular system in patients with SLE. For the heart, these include echocardiography [68,69], left ventricle angiography (conventional and Technetium-99 m myocardial perfusion imaging) [70], cardiac magnetic resonance imaging [69] and electron beam CT. The latter method quantifies coronary artery calcification, which is an indirect marker of coronary atherosclerosis [8,71]. A detailed description of these imaging techniques is beyond the scope of this chapter, but we have reviewed this field elsewhere [72].

For the arterial tree, ultrasound assessment of carotid atherosclerosis is an accurate, non-invasive method that allows for the assessment of arterial wall thickness and degree of plaque. Manzi *et al.* studied the prevalence of carotid atherosclerosis as measured by B-mode ultrasound in 175 women with SLE, finding that 40% had at least one focal plaque and that more than 20% had at least one large plaque (>50% of the vessel diameter) or multiple plaques with at least one medium plaque (30%–50% of the vessel diameter). Patients with higher cumulative damage measured by the modified SLICC damage score were more likely to have plaque, even after excluding the cardiovascular components of the SLICC index. A strong association between the duration of use and cumulative dose of corticosteroids was also found [18]. These findings were echoed by other studies, which also suggested that plaque progression among patients with SLE was accelerated and that the presence of plaque predicted the occurrence of future CVD-related events [9,73,74]. Further enhancement of ultrasound assessment of carotid plaques can be achieved using integrated backscatter analysis of carotid-intima complex, which appears to correlate with calcium and collagen content of vascular wall, therefore non-invasively evaluating arterial sclerosis [75,76]. There is an argument that the femoral arteries should also be scanned because in non-SLE patients, femoral plaque is also associated with increased risk of coronary disease [77]. In our recent ultrasound study of 100 patients, we found that 7/36 patients with plaque only had it in the femoral arteries and not in the carotids [67].

An alternative method to ultrasound is high-resolution CT angiography, which focuses essentially on providing improved accuracy and sensitivity and allows for a 'virtual' histology of plaques as it has been shown to correlate with histological findings of atheromatous plaques at the carotid bifurcation [78]. However, limitations associated with the use of contrast and radiation exposure are of concern.

Currently, none of these methods are used in routine clinical practice to estimate CVD risk in patients with SLE. Carotid ultrasound is the most likely to come into use soonest on the basis of cost, safety, and accumulation of previous data.

Summary

CVD, principally coronary heart disease and stroke, is one of the most important causes of morbidity and mortality in patients with SLE. The risk of developing CVD is elevated in patients with SLE. This is partly, but not wholly, due to traditional CVD risk factors such as hypertension, smoking and elevated lipid levels, so it is important for clinicians to address these factors. However, standard risk calculators based on the Framingham equations cannot be used to predict which patients with SLE are at highest risk of CVD. These calculators underestimate CVD risk in patients with SLE because some of this risk is due to non-traditional factors such as immune dysfunction. There have been moves to develop SLE-specific CVD risk algorithms incorporating novel biomarkers, but none are in widespread clinical use. It is also possible that non-invasive imaging such as vascular ultrasound could be used in future to visualise atherosclerotic plaque in asymptomatic patients and thus guide the management of CVD risk.

The underlying causes of the increased CVD risk in patients with SLE are not fully understood. However, evidence suggests that both abnormal serum lipid profile and abnormal immune response to lipids contribute. In particular, raised VLDL, dysfunctional HDL, and changes in the number and phenotype of *i*NKT cells have been demonstrated to show associations with presence and/or progression of atherosclerosis. These findings may be used to improve both assessment and management of CVD risk in patients with SLE in the future.

Practice points

- Patients with SLE have an increased risk of developing CVD.
- It is important to consider whether smoking, diabetes, blood pressure and lipids are under optimal management in patients with SLE.
- However, the standard CVD risk calculation algorithms underestimate the risk in patients with SLE.

Research agenda

- It is important to develop SLE-specific CVD risk algorithms that include factors known to influence this risk in patients with SLE.
- Levels of VLDL and d-HDL may be important contributors to CVD risk in patients with SLE.
- *i*NKT cells appear to adopt an atheroprotective phenotype in patients with SLE and asymptomatic atherosclerotic plaque and lose this phenotype when CVD develops. Further experiments to understand this phenomenon are needed.

Conflict of interest

Neither author has any conflicts of interest.

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