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Atherosclerosis in systemic lupus erythematosus

Sara Croca, Anisur Rahman*

Centre for Rheumatology Research, Division of Medicine, University College London, Room 412 Rayne Institute, 5 University Street, London WC1E 6JF, United Kingdom

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A B S T R A C T

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.

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

* Corresponding author.
E-mail addresses: saracroca@gmail.com (S. Croca), anisur.rahman@ucl.ac.uk (A. Rahman).

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[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 undertreated with steroids, which could imply that poorer disease control is more relevant in determining a higher CVD risk than steroid treatment *per se* [8].

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