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Atherosclerosis in Systemic Lupus Erythematosus: An Ongoing Challenge

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Abstract

Premature atherosclerotic cardiovascular disease (CVD) is a common and devastating complication of systemic lupus erythematosus (SLE, lupus) leading to myocardial infarction and stroke. Young women and men with systemic lupus erythematosus have strikingly high rates of coronary heart disease. Traditional risk factors do not fully explain the excessive cardiovascular events observed in SLE. During atherosclerosis, macrophage-driven inflammation leads to progressive damage characterized by accrual of lipid and fibrous elements in the vessel wall. Persistent immune system activation is likely key to acceleration of atherosclerosis in SLE, although SLE disease activity markers cannot predict cardiovascular risk, nor can Framingham risk factors. Strategies to treat and prevent CVD in lupus include statins and medications to control traditional CVD risk factors. However, these are insufficient with low success. While statins are a mainstay treatment for CVD in the general population, CVD in SLE is resistant to statins. This brief review explores the factors that set apart atherosclerotic CVD in lupus from the process in the general population.

Introduction

Systemic lupus erythematosus is a multisystem autoimmune rheumatic disease characterized by periods of exacerbation and remission [1] (Table 1). Breakdown of immunological self-tolerance manifests as autoantibody production and immune complex deposition. Both the innate and adaptive immune system are dysregulated. Autoantibody-producing B cells secrete inflammatory cytokines and, by presenting autoantigens, activate T cells [2]. Many organs can be affected, most commonly joints, skin, cardiovascular system, nervous system, kidneys and bone marrow [3]. SLE mainly affects young women during their childbearing years, and is found more commonly in minority populations [4,5]. Management is generally through the use of corticosteroids, antimalarials and immunosuppressive drugs [6,7] The human monoclonal antibody belimumab is specific for B-cell-activating factor, a B cell-regulating cytokine that is elevated in SLE. Belimumab is approved in the USA, Canada, Europe and other countries to treat adult SLE patients with mild–moderate active disease despite standard therapy [8].

Cardiovascular disease (CVD) causes significant excess morbidity and mortality in lupus patients relative to the general population [9-11]. Atherosclerotic CVD occurs earlier and more frequently in SLE, particularly in young women, a group normally relatively free of atherosclerosis [12-14]. Mortality from myocardial infarction in SLE is 10 times greater than in age-matched controls. Atherosclerosis contributes to about 30% of deaths in SLE and about 30% of lupus patients have subclinical atherosclerosis [15-17]. The dramatic excess in cardiovascular morbidity and mortality in young people with lupus is not explained by traditional risk factors or medication use.

Table 1. Systemic lupus erythematosus. General features

Systemic Lupus Erythematosus
Connective tissue related chronic inflammatory and autoimmune disorder
Immune complex and autoantibody-mediated tissue injury
Primarily affects pre-menopausal females
Heart, lungs, kidneys, joints are primary targets
Premature atherosclerotic CVD is the most common form of cardiovascular damage
Common symptoms: malar rash, fatigue, joint pain/swelling, headaches, anemia, fever

Explaining the Excess CVD Risk

Lupus accelerates atherosclerosis, suggesting that immunologic factors impact atherogenesis in the autoimmune setting [18]. However, the precise pathophysiologic mechanism(s) that link SLE to atherosclerotic CVD are not known and SLE disease activity markers cannot predict CVD risk, nor can Framingham risk factors [19-21]. Known risk factors for atherosclerotic CVD that occur with greater frequency in SLE patients than in the general population include corticosteroid-induced hypercholesterolemia and hypertension associated with renal disease (Table 2). However, even in studies controlling for steroid therapy and renal disease, the association between SLE and accelerated atherosclerosis remains [21,22].

The pathogenesis of atherosclerosis involves interplay between cholesterol metabolism and cellular inflammatory pathways [23-25]. Persons with lupus exhibit elevated levels of cytokines, most notably type I interferons, and inflammatory mediators that can accelerate development of atherosclerosis by promoting cholesterol accumulation in macrophages and endothelial cells [13,26,27]. Lipid overload leads

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to macrophage transformation into plaque-forming foam cell—a hallmark of atherosclerosis (Figure 1) [28]. In lupus, blood vessel inflammation results from autoimmunological endothelial activation [29]. Endothelial activation with breach of the monolayer, initiating factors in atherosclerosis, are associated with Type I interferons in SLE [30,31]. Activated endothelium expresses adhesion molecules, chemokines, and cytokines and recruits circulating monocytes in a multi-step process that involves sequential capture, rolling and adhesion, followed by transmigration and differentiation into macrophages.

Atherosclerosis in SLE, as in the general population, is histologically a disease of cholesterol accumulation in the arterial wall [32,33]. Current research focuses on the impact of inflammation and how it might be controlled. However, attempts to correlate CVD risk with autoimmune disease activity have been unsuccessful and, other than recognition of dyslipidemia as a risk factor, cholesterol metabolism has been largely ignored.

Routine lipid measurements do not distinguish between lupus and normal controls, nor do they help identify lupus patients with atherosclerosis [34]. LDL measurement is of limited value in CVD risk assessment for patients with SLE [35]. Lupus does cause disruptions in lipid metabolism and homeostasis, notably changes in quality of high density lipoprotein (HDL) with structural and functional abnormalities. Some studies show low circulating HDL levels as well [36,37]. Dysfunctional HDL that has lost its anti-inflammatory and atheroprotective properties has been observed in SLE [38].

Our group has used an in vitro cell culture approach to look at atherogenic properties of lupus plasma. We reported that cultured THP-1 human macrophages, a pertinent model of atherosclerosis, exposed to plasma from SLE patients manifest a pattern of disturbance

Table 2. Atherosclerotic risk factors in systemic lupus erythematosus. Traditional and non-traditional

Atherosclerotic Risk Factors: Systemic Lupus Erythematosus	
Traditional	**Non-Traditional**
Age	SLE disease activity
Sex	SLE disease duration
Obesity	Cumulative damage
Diabetes	Autoantibody levels
Smoking	Inflammatory markers (cytokines, high sensitivity C-reactive protein)
Hypertension	Use of steroids
Hyperlipidemia	Use of cyclo-oxygenase inhibitors

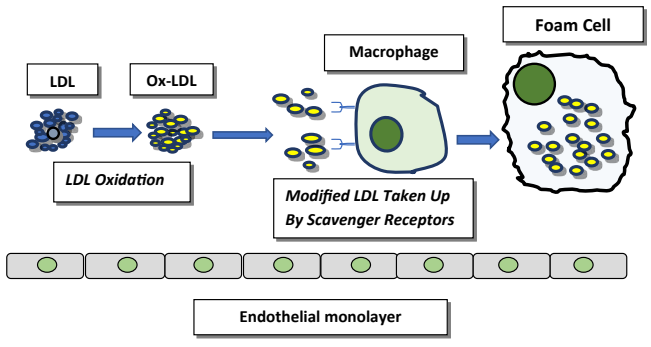

Figure 1. Foam cell formation. LDL particles (blue) become oxidized in the vascular wall. Oxidatively modified LDL (Ox-LDL, yellow) is then taken up by scavenger receptors on the macrophage cell surface. The internalized Ox-LDL accumulates inside the macrophage, transforming it into an atherogenic foam cell

in expression of genes involved in lipid transport that is atheroma-promoting. When THP-1 macrophages are exposed to lupus plasma, key proteins that prevent lipid overload are suppressed. These cholesterol efflux proteins are 27-hydroxylase and ATP binding cassette transporter (ABC)A1. In addition, the scavenger receptor CD36 that facilitates cholesterol uptake is augmented, leading to increased foam cell formation [39,40]. These results indicate that compared to healthy controls, SLE patients exhibit pro-atherogenic differences in cholesterol transport, encouraging lipid accumulation. Macrophage cholesterol homeostasis, a delicate balance among influx, endogenous synthesis, esterification/hydrolysis and efflux, is disrupted in the lupus environment, likely due to immune and inflammatory mediators and cytokines such as interferon-γ [41,42].

While more advanced therapies have decreased mortality from lupus disease activity, deaths from atherosclerotic CVD in SLE have not declined [43]. An understanding of the underlying processes could lead to improved prediction of who among persons with lupus are at highest risk for developing CVD. At this time, prediction tools are lacking for the SLE population. Readily available assessments of atherosclerotic risk would be an invaluable tool for monitoring disease state and responsiveness to therapeutic interventions. McMahon, *et al.* [44] have assembled a biomarker Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE (PREDICTS) based on proinflammatory HDL, plasma levels of leptin, homocysteine, and soluble TNF-like weak inducer of apoptosis as well as age, and diabetes. Even more recently, López, *et al.* [45] propose utilizing levels of anti-PON1 and anti-HDL antibodies in serum as biomarkers of endothelial damage and premature atherosclerosis in SLE. Imaging studies show some promise. Carotid artery Doppler ultrasound with measurement of both intima-media thickness and total plaque area, was shown to independently predict cardiovascular events [46-48]. Understanding pathogenesis and predicting risk are high priority so that effective interventions can be implemented [49].

Current Treatment Approaches

The traditional approach to atherosclerotic CVD therapy in SLE consists of lifestyle improvements and treatment of risk factors, mainly hypercholesterolemia. Drug regimens designed to lessen traditional risk factors may include antiplatelet agents, antihypertensives, anticoagulants, and, most commonly, statins [50,51]. Treatment with lipid-lowering statins, the first-line of therapy for atherosclerotic CVD is insufficient and cardiovascular morbidity and mortality in SLE patients remains inordinately high [52,53]. In the Lupus Atherosclerosis Prevention Study (LAPS), Petri, *et al.* [54] showed that the HMG CoA reductase inhibitor atorvastatin failed to reduce subclinical measures of atherosclerosis or disease activity over 2 years in SLE patients.

Conclusions and the Future

Our ability to predict who is at risk for CVD in the lupus population is limited and underestimated. Multiple aspects of the risk assessment and management program for atherosclerotic CVD in the general population do not work well in the SLE population. Our capacity to prevent development and progression of atherosclerosis is inadequate. Lifestyle modification and control of disease activity aimed at reducing inflammation are desirable, but insufficient. Despite optimal standard-of-care lipid lowering regimens, residual morbidity and mortality remains high. The value of statins is unclear, but appears to be less than in the general population. SLE is an independent risk factor for post-myocardial infarction mortality [55]. Unless new

treatment approaches are developed, ASCVD is expected to cause an increasing proportion of the mortality in the lupus population.

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Conflict of Interest

All authors have read the journal's authorship agreement and policy on disclosure of potential conflicts of interest and the authors declare no conflicts of interest.

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