

Atherosclerosis in Systemic Lupus Erythematosus – Epidemiology, Risk Factors, Subclinical Assessment and Future Study

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Abstract

Over the last 40 years, it has become established that patients with Systemic Lupus Erythematosus (SLE) have a greater risk of atherosclerosis and related events compared with the general population of similar age and sex. While the precise mechanisms that cause accelerated atherosclerosis in SLE remain undetermined, much evidence from inception and prospective longitudinal studies suggests a role for traditional cardiovascular disease and lupus-specific risk factors, systemic inflammation and lupus-directed therapies. This review will summarize much of the important knowledge available in the medical literature on this topic.

Keywords: Systemic lupus erythematosus; Atherosclerosis; Cardiovascular disease; Subclinical atherosclerosis; Corticosteroids; Antimalarial; Risk factors

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multi-system autoimmune disease with a predilection for females, with a female-to-male ratio of between 4.3 and 13.6 [1], and a mean age at diagnosis of 34.3 years [2].

Atherosclerosis is a pathological inflammatory process of the artery, primarily affecting the intima, involving a complex interplay of endothelial dysfunction, monocyte and T-lymphocyte intimal invasion and inflammatory cytokine production, producing lesions known as atheromata that are responsible for infarction of target organs, through occlusion of the affected vessel [3]. Myocardial Infarction (MI), stroke and critical limb ischemia are all end-stage consequences of progressive atherosclerosis, termed Cardiovascular Disease (CVD). The 'traditional risk factors' for CVD have been identified from longitudinal studies on a population from Framingham in the USA, and include increasing age, male sex, hypertension, smoking, dyslipidemia and diabetes mellitus [4].

Despite their relative youth and the predominance of the female sex, patients with SLE have a pronounced risk for accelerated atherosclerosis. The precise mechanisms for the development of premature atherosclerosis remain elusive but an increasing volume of evidence suggests that combinations of traditional CVD risk factors with lupus-specific and treatment-related variables are important contributors to this process.

Since the 1970s, the University of Toronto Lupus Clinic (UTLC) has prospectively gathered data on all of our lupus patients, through regular follow-up (every 2 to 6 months) using a detailed protocol that captures recent disease activity and organ damage accrual, along with laboratory testing for dyslipidemia, hyperglycemia and serological markers of lupus activity. The UTLC has the largest, longest-followed single-centre cohort of SLE patients which has allowed detailed examination of CVD in lupus.

This review will summarize much of the important evidence available, from the UTLC and other international centres, with the intent of stimulating interest and hypothesis-generation in the advancement of knowledge in this field.

Epidemiology of Atherosclerosis in SLE

The association between atherosclerosis and SLE was first suggested in a case report in 1964 [5]. A bimodal pattern of mortality in SLE was then identified in 1976, with a proportion of patients dying from sepsis within the first year of diagnosis and another group of patients dying later in their disease course, with myocardial infarction the cause of death in 80% [6].

Since the 1970s, improved survival rates in SLE patients have resulted in an increase in disease duration with the concomitant accrual of organ damage. Cardiovascular disease accounts for nearly 30% of the organ damage suffered by patients with lupus for 15 years [7].

Of surviving patients from inception into the UTLC between 1970 and 1978, 27.6% had coronary artery disease (CAD) 24 years later [8]. Within the first year of diagnosis, the cardiovascular system was the organ system most often damaged (10% of the cohort) [7]. The cross-sectional prevalence of atherosclerosis-related vascular events amongst almost 1100 lupus patients followed over 4 decades from 1970 was 11%, and 10% in 561 inception patients [9]. These events occurred at a mean of 8 to 9 years from the time of diagnosis [9].

The 10-year risk of CAD-related events in SLE is between 13 and 15% [10] while the estimated relative risk of CVD is between 5 and 8 times that of the general population [11].

The average age of a first CAD-related event in females with SLE is between 48 and 50 [12], compared with a median age of 65 in those without lupus [13]. The age-difference at the time of CVD-related death is, on average, 14.8 years for females and 11 years for males [14].

Premature CVD is more common in premenopausal women with

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SLE than in similarly age-matched females without SLE, while females with lupus aged between 35 to 44 have a risk of MI 52 times that of non-lupus females of similar age [15]. The incidence of CVD events in those fewer than 40 years of age is 5.3 times the expected rate as calculated by the Framingham risk model [16].

Racial differences in atherosclerotic risk in SLE

Compared with Caucasians, African American females develop SLE at a younger age; have more aggressive disease at onset and a higher frequency of renal disease [17].

In a retrospective study from South Carolina, compared with Caucasians, African Americans were found to have greater 1-year mortality after hospital discharge, more emergent admissions, greater levels of co-morbidity and die at a younger age, combined with an evident disparity in private health care insurance and income [18].

Scalzi et al. found that black female and male patients with SLE, compared to the corresponding sex in whites, were on average 9.6 and 10.7 years younger at the time of hospital admission for CVD, while Hispanic females and males were 6 and 11.6 years younger than whites (all p values < 0.0001) [14]. Furthermore, black females with SLE were an average of 14.3 years younger than white female SLE patients at the time of CVD-related death ($p < 0.0001$), and black males 13.9 years younger ($p = 0.06$). Socioeconomic variables were not included in this analysis.

In a previous study, Scalzi et al. [14] found that, amongst African American SLE patients, smokers had greater mean carotid intima-media thickness, a marker of sub-clinical vascular disease, than non-smokers, a finding not observed in the Caucasian group, while lipid-lowering medication use was less prevalent in African Americans (0% v 22%, $p = 0.007$) [19]. In contrast, the Hopkins Lupus Cohort Study found that 15% of black and 14% of white patients had carotid plaque, in the absence of previous CVD events [20].

The Lupus in Minorities, Nature vs. nurture (LUMINA) multiethnic lupus cohort is a longitudinal study of outcome comprised of African-American, Caucasian and Hispanic SLE patients studied in the United States of America. This group found no difference in the incidence of atherosclerotic vascular events after baseline entry into the cohort among the 3 ethnicities [21]; however, they found that the CRP gene variant, GT20, was more prevalent in African American and Hispanic patients and that carriers of this polymorphism have greater risk for developing CVD events [22] and that a mannose-binding lectin-deficient genotype was associated with cerebrovascular events in Caucasians only [23].

Together, these findings suggest that ethnic differences in SLE and atherosclerosis exist and are multifactorial in nature, and may be accounted for by diversity of genotype, socioeconomic disparity and environmental exposure.

Assessing Subclinical Atherosclerosis

A number of surrogate markers for atherosclerosis have been examined in lupus and demonstrate that vascular damage in SLE occurs at an accelerated rate.

Endothelial cell dysfunction

The pathogenesis of atherosclerosis begins with Endothelial Cell (EC) dysfunction. Flow-mediated vasodilation (FMD) is a non-invasive method employing ultrasound to evaluate such dysfunction [24]. In the general population, abnormal FMD is seen in patients with CAD and

those with risk factors for CVD events [25]. Lupus patients without a history of CVD have been shown to have reduced FMD [26]. Lima et al. found significantly impaired FMD in 69 pre-menopausal SLE patients compared with 35 age- and sex-matched controls, and this impairment remained in a sub-group without any traditional CVD risk factors [27].

Coronary artery calcification

Electron beam Computed Tomography (CT) allows the quantification of Coronary Artery Calcification (CAC). Compared with conventional coronary angiography, this has been shown, in the general population, to have a sensitivity of 92% for coronary stenosis of 50% or greater, with a moderate specificity of 51% [28]. CAC is an independent predictor of all-cause mortality [29] and a potent predictor of myocardial perfusion deficit [30].

In SLE, Manger and colleagues have shown that 28% of patients aged between 20 and 48 had CAC [31], compared with 1% of the non-lupus female population under 50 years of age [32]. In their study, smoking, cumulative corticosteroid intake, renal impairment and a high complement 3 (C3) were independent predictors of CAC.

Asanuma et al. [33] found that the prevalence of CAC in SLE patients without a history of CVD was 31%, compared with 9% of controls, and that CAC occurred at a younger age (7% vs. 0% in those under 40). CAC increased in prevalence with advancing age (78% of 50-59 year olds vs. 21% of controls of the same age) [33]. No lupus-specific or traditional CVD risk factors predictive of CAC were found in this study.

In 200 SLE patients without a previous history of CVD, Kiani et al. found CAC in 43%, and that age, Body Mass Index (BMI) and diabetes mellitus were all predictors of CAC [34].

Calcification of arterial plaque is reflective of the latter stages of plaque evolution less propensities to rupture. CAC alone is not reflective of the absolute burden of atherosclerosis and studies from the general population suggest non-calcified coronary plaque (NCP) may be more important [35,36]. In SLE, multi-detector CT technology has shown that 53% (N=52/99) of patients without CAC have evidence of NCP, compared to 96% of patients with CAC [37]. Studies from the general population, however, suggest a much lower prevalence of NCP, where 6.5 to 16% have NCP in the absence of CAC [38,39], again demonstrating the greater burden of atherosclerosis in SLE.

Carotid intima-media thickness and plaque

Quantification of the intima-media thickness in the Carotid Artery (CIMT) using ultrasonography has been used as a surrogate for atherosclerosis in both the general population and the rheumatic diseases, including lupus. De de Leeuw and colleagues longitudinal case-control study examining the risk factors for progression of CIMT in SLE found CIMT was significantly greater in lupus patients at baseline and in those aged over 30 years [40]. CIMT progression, defined as an IMT increase of greater than 0.03 mm, was evident in 40% (N=21) of patients studied at follow-up after a mean of 32 months, while age was the only baseline variable independently predictive of CIMT progression.

CIMT measurement is both non-invasive and relatively affordable and, as a result, has been favoured by investigators as a bedside tool in the characterization of CVD risk. However, limitations to CIMT use as a surrogate for atherosclerosis are significant, and need to be taken into account. In the general population, while CIMT correlates with the severity and extent of coronary atherosclerosis, its use as a predictor of CAD is weaker compared with other predictors such

as age, male sex and diabetes [41]. The CIMT may reflect reactions to hemodynamic changes such as increases in blood pressure or age [41,42] rather than underlying atherosclerosis. Furthermore, the rate of arterial plaque progression has been shown to be double that of the change in IMT, and plaque may be a better predictor of future CVD events than IMT [43]. Traditional CVD risk factors account for only 15 to 17% of the IMT [42], compared to over 50% of total plaque area [44]. It has been suggested that use of CIMT as a marker of progression of atherosclerosis would require a mean difference of 1.4mm to be observed before recognition by a sonographer [45].

These issues with CIMT as a predictor and surrogate of atherosclerosis have led to the examination of carotid plaque, again using ultrasound, as a more robust surrogate.

Roman and colleagues examined the prevalence and correlates of carotid plaque and CIMT in SLE patients, using a case-control study design, matching cases (N=197) and controls (N=197) for age, sex, race and hypertension status [46]. Plaque was significantly more prevalent in SLE patients in every age group (relative risk 2.4, CI 1.7-3.6; $p<0.001$), whereas CIMT was significantly less in patients than controls. The authors, did however, include a small group with CAD (3.9% of the SLE population). Overall, 37.1% of SLE patients had evidence of plaque compared with 15.2% of controls ($p<0.001$). In the SLE group (compared with controls), plaque was present in 13.4% (vs. 2.4%, $p=0.009$) of patients less than 40 years if age, 33% (vs. 13.2%, $p=0.01$) of patients in the 5th decade of life, 72.5% (vs. 30%, $p<0.001$) in the 6th decade and 71.4% (vs. 45%, $p=0.08$) in the 7th or greater decade. The presence of lupus (OR 4.8, CI 2.6-8.7), age and serum cholesterol level were independently associated with plaque in a multivariate analysis, while in lupus patients alone, an older age at diagnosis, a longer disease duration, a higher damage-index score (Systemic Lupus International Collaborating Clinics-Damage Index, or SDI) and the absence of use of cyclophosphamide were independent predictors of plaque.

This work was extended by examining baseline variables associated with plaque progression from 158 of the lupus patients reported on above. Of the 158 patients, 45 (28%) had progression of carotid plaque over a mean interval of 34 months, while almost 50% had persistent absence of carotid plaque [47]. The age at diagnosis (OR 2.75, CI 1.67-4.54), duration of SLE (OR 3.16, CI 1.64-6.07) and baseline homocysteine concentration (OR 3.14, CI 1.65-5.95) were independently predictive of atherosclerosis progression. The authors assert that the per-year rate of plaque progression (10%) in this study is substantially higher than that seen in the general population (<5%).

Selzer et al. from the Pittsburgh Lupus Registry, examined the relationship between traditional CVD risk factors and the presence of carotid plaque in lupus patients without a history of vascular disease [48]. From 214 female patients, 34% had plaque, with age (OR 1.12, CI 1.07-1.17), systolic BP (OR 1.03, CI 1.01-1.06) and HDL (OR 0.96, CI 0.93-0.99) independent predictors of plaque on multivariate regression analysis.

The Pittsburgh group compared the progression of plaque and CIMT from baseline over an average of 4 years, in 217 patients with SLE and a healthy control group (N=104) [49]. Almost 30% of SLE patients had evidence of plaque progression, compared with 10% in the control group, with age, triglyceride level, higher C3 and immunosuppressant use at baseline all predictive of an increase in plaque severity. Interestingly, CIMT progression was similar in both the lupus and control groups, suggesting that carotid plaque may be a better surrogate and outcome measure of atherosclerosis in SLE.

The Hopkins Lupus Cohort Study reported that, of 605 inception

patients studied, 85 (14%) had carotid plaque [20], while Ahmad et al. found that, in SLE patients and controls (both <55 years old), plaque was present in 21% compared with 3%, respectively [50]. Furthermore, SLE patients had plaque at lower IMT levels than controls. At the UTLC, we have found that the total carotid plaque area is a much stronger predictor of CAD compared with CIMT (OR 9.55, CI 3.46-26.39 vs. OR 2.87, CI 1.65-5.02) in a cross-sectional study comparing SLE patients with (N=27) and without (N=76) a history of CAD (manuscript in preparation; pilot study presented in abstract format [51]. Of those with CAD, 89% had carotid plaque, while there was a moderate correlation ($r=0.43$, $p<0.001$) only between CIMT and plaque area, suggesting different phenotypes of atherosclerosis.

The available evidence regarding CIMT and carotid plaque suggests that plaque and IMT arise through different mechanisms and/or are influenced by different factors. Carotid plaque may have greater utility than CIMT as a surrogate of atherosclerosis in SLE.

Myocardial perfusion

Data from the UTLC has shown that 35% of female SLE patients with no history of CAD have evidence of myocardial perfusion defects, as defined by Single Photon Emission Computed Tomography (SPECT) Dual Isotope Myocardial Perfusion Imaging (DIMPI) [52]. Furthermore, among patients with symptoms of CAD, 45% have normal coronary angiography, while 58% have myocardial perfusion defects despite normal angiography [53]. These findings suggest that mechanisms other than plaque formation and vessel stenosis, such as coronary vasospasm or small vessel disease, may account for the increase in CAD-related events in SLE.

The imaging modality with greatest predictive value for Atherosclerotic Vascular Events (AVE) remains to be ascertained. However, an imaging modality alone is unlikely to confer the entire risk of AVE. The challenge for clinicians is in the identification of all individual factors, including those gleaned from imaging technology, that collectively allow the most accurate risk prediction. In that regard, traditional CVD risk factors and those specific to lupus have relevant roles.

Role of Traditional Risk Factors

The University of Toronto Lupus Clinic

The UTLC has reported a number of findings regarding the prevalence and influence of traditional and lupus-specific risk factors on AVEs in SLE.

Bruce et al. reported that 75% of SLE patients from the UTLC had hypercholesterolemia, defined as raised total serum cholesterol, within 3 years of their diagnosis, with 40% having a sustained rise in total cholesterol over the first 3 years of their disease [54]. Of those that subsequently developed CAD-related events, nearly 80% occurred in those with a sustained increase in total cholesterol in the first 3 years of SLE.

Smoking was the only traditional CVD risk factor independently predictive of an AVE (RR 3.28, CI 1.14-9.43) in an SLE cohort (N=561) studied from inception (those that presented to the UTLC within 12 months of diagnosis). Similar to the LUMINA group's findings [21], the number of traditional risk factors was greater in those with an AVE than those without (2.2 ± 0.9 vs 1.8 ± 1.0 ; $p=0.04$) [9]. Despite this difference, the Framingham risk score (FRS) for CAD in the inception cohort was similar in both groups (AVE vs. no AVE), reducing its utility as a predictor of CAD risk. Of note, neuropsychiatric lupus was

also an independent predictor of AVEs in the inception cohort (RR 3.7, CI 1.33-10.32) and the total cohort (N=1087, combining inception and non-inception cohorts), while vasculitis (RR 2.26, CI 1.22-4.17) and the number of traditional risk factors (RR 1.76, CI 1.26-2.47) were also independent predictors of AVE in the total cohort.

The UTLC reported on the prevalence of traditional CVD risk factors in 250 SLE female patients from the UTLC (mean disease duration 13.7 ± 9.7 years) age and sex-matched with healthy controls [55]. For a female population of relatively young mean age (44.8 ± 12 years), those with SLE had greater prevalence of hypertension and diabetes mellitus, yet despite having a higher mean number of risk factors, their Framingham 10-year risk score for a future CAD event was the same as the control population, at 3.2%.

Goldberg et al. [11] found that, in a multivariate analysis of predictors of CAD in both lupus patients and controls, SLE was independently predictive with a hazard ratio of 4.2 (CI 1.49 – 11.97; $p=0.007$), along with age and triglyceride level or metabolic syndrome. Patients were compared to an age and sex-matched control population and both were followed for an average of 7 years. The occurrence of CAD was greater in SLE (7%) compared with controls (2%; $p=0.01$). While previous work on this cohort had shown that SLE patients have higher levels of VLDL, triglycerides, homocysteine, and waist:hip ratio, with more patients in a post-menopausal state and a more sedentary lifestyle, with hypertension and diabetes [55], only the post-menopausal state was associated with CAD on univariate analysis in this study [11]. In addition, SLE patients who developed CAD were significantly older at baseline (54 ± 12 years) than those without CAD (44 ± 12 years; $p=0.002$), had greater steroid use at baseline (82% vs. 53%; $p=0.02$) and significantly greater baseline CRP levels. The FRS at baseline in those who went on to develop CAD was higher than those who did not (2.9 ± 4 vs. 5.8 ± 4.2 ; $p=0.004$), despite the magnitude of the CAD 10-year risk being clinically insignificant. Furthermore, the number of Framingham risk factors was similar in both SLE groups (CAD vs. no CAD), while in controls, the number of risk factors was significantly greater in those that developed CAD, compared to controls who did not.

Other groups have also examined the role of traditional risk factors on AVE risk in SLE.

Esdaile et al. examined the prevalence of the Framingham risk factors in a retrospective analysis of SLE patients (N=263) followed for a mean of 8.6 years [56]. At baseline entry into their registry, older age, cholesterol, systolic and diastolic blood pressure was associated with future CVD events on univariate analysis. Importantly, the authors found that the FRS underestimates the risk of stroke and CAD in lupus by a factor of 7.9 and 7.5 respectively, strongly suggesting that there are lupus-specific factors responsible for accelerated atherosclerosis in SLE.

Magder and Petri, in a pooled logistic regression analysis of the Hopkins Lupus Cohort (N=1873), determined that the rate of cardiovascular events (CVE) in SLE was 2.7 times higher than would be predicted for the general population based on the Framingham Risk Formula [16]. Multivariate analysis revealed that older age (rate ratio (RR) 1.6, CI 1.4-1.9), male sex (RR 1.6, CI 1.01-2.7), mean systolic blood pressure (RR 1.2, CI 1.02-1.35), mean past total cholesterol (RR 1.04, CI 1.01-1.08), a history of lupus anticoagulant (RR 1.7, CI 1.22-2.47), current corticosteroid dose of ≥ 20 mg (RR 2.5, CI 1.44-4.48) and recent presence of anti-double stranded DNA antibody (anti-dsDNA) (RR 1.56, CI 1.05-2.31) were all independent predictors of CVE.

Research from Manchester (UK) has shown that risk factor models composed of lupus-specific variables only, rather than traditional CVD

risk factors, more accurately predict the presence of atherosclerosis in SLE, using carotid plaque as a surrogate [50]. In a control population (N=100) using age, pack years of smoking and systolic blood pressure in a multivariable model to predict atherosclerosis, the Area Under The Curve (AUC) was 0.90 compared with 0.75 in the SLE cohort (N=200) ($p<0.01$). Lupus-specific factors that were significantly associated with plaque and yielded the greatest AUC when included in the regression models for SLE were: older age at diagnosis, disease duration, and higher neutrophil count, azathioprine use and anticardiolipin antibodies (AUC 0.87). The AUC for lupus-specific factors was significantly greater than that using traditional risk factors alone (0.87 vs. 0.75, $p<0.01$).

The SLICC registry for atherosclerosis

The Systemic Lupus International Collaborating Clinics (SLICC) is a group of SLE experts from 33 centres across 12 countries (in North America, Europe and Asia) that has developed an international registry of newly diagnosed lupus patients of multiple ethnicities, enabling the prospective study of CAD with regard to its incidence, prevalence, and the contribution of associated risk factors [57]. This registry reported that, of 918 patients with SLE for less than 15 months, 33% had hypertension, 36% hypercholesterolemia, 16% were current smokers, 15% were post-menopausal and nearly 4% had diabetes at the time of enrolment. The collective prevalence of these traditional CVD risk factors is notable given the youthful mean age at diagnosis of just 34.1 ± 13.5 years in a group composed primarily of women (89%). Of further interest was the finding that the mean Framingham 10-year CAD risk score was low at 2.55 ± 3.38 at inception, compared with the original Framingham inception cohort (3.29 ± 4.5) with the same age and gender distribution. Once again, these findings suggest that lupus-specific risk factors have a prominent role in the pathogenesis of accelerated atherosclerosis.

Over the following 3 years after enrolment, the prevalence of traditional CVD risk factors increased, with 58% of patients having hypertension after 3 years and 60% having hypercholesterolemia with only a modest increase in the use of corticosteroids (12%) over the 3 year period [58]. The percentage increase from enrollment for hypertension was 49%, with 65% for hypercholesterolemia, 37% for smoking, 56% for diabetes and 37% for the post-menopausal state. Therefore, traditional risk factors accumulate in a relatively short time period after diagnosis of SLE and close monitoring of traditional CVD risk factors is warranted in SLE even in the early years of disease.

After 8 years of follow-up from inception, the SLICC group reported their findings on AVE [2]. When the baseline characteristics of those patients with an AVE (N=22) were compared to those without (N=615), white ethnicity, male sex, older age at diagnosis, hypertension, obesity, smoking and a family history of CAD were all associated with an AVE; however, only older age at diagnosis (OR 1.08, CI 1.05-1.11) and male sex (OR 3.67, CI 1.41-9.52) were independently predictive of an AVE on multivariate analysis. While men made up only 11% of the inception cohort, they accounted for 41% of the patients with an AVE.

While data from inception longitudinal cohort analyses has advanced insight into the role of traditional risk factors in lupus-associated CVD, a limitation of the existing literature, regarding the predictive ability of individual CVD risk variables for future AVE, is that data are captured at single time points and are not reflective of the effect that variance in such variables over time might have on CVD risk.

Nikpour et al. addressed this issue by characterizing the variability,

over a mean time of 9.3 years, of total serum cholesterol and blood pressure in 1,260 SLE patients [59]. Over time, 65% of patients had fluctuations in their total cholesterol levels and 46% in their blood pressure (BP). Furthermore, coincident disease activity (SLEDAI-2K) and age were independent correlates of both cholesterol and BP. Corticosteroids were independently predictive of coincident cholesterol level, while antimalarial use was a significant negative correlate of coincident cholesterol level. These findings demonstrate that fluctuations in these two traditional CVD risk factors in SLE are associated with both disease activity and the therapies prescribed, and suggest that incremental insults by these factors could partially account for the acceleration of atherosclerosis in SLE.

This work was extended to examine measures of cumulative exposure of total cholesterol and blood pressure in quantifying the risk of CAD in SLE [60]. Unlike the Framingham risk model, single incident cholesterol or BP readings were not predictive of CAD, but rather time-adjusted mean values were. Furthermore, disease activity and corticosteroid use significantly increased the risk of CAD while antimalarial use was protective.

In summary, SLE is an independent risk factor for future CVD events. However, patients with lupus are at increased risk of acquiring traditional risk factors for CVD, despite their relative youth. Corticosteroid use may account for some of this excess risk. While the Framingham risk score underestimates the 10 year risk of future CVD events in SLE, traditional risk factors should not be ignored and treatment of SLE should aim to optimize control of cholesterol, BP, glucose and smoking cessation.

Metabolic syndrome

The Metabolic Syndrome (MeS) is a combination of traditional CVD risk factors associated with insulin resistance (IR), an elevated risk of developing type II diabetes mellitus and atherosclerosis. The syndrome considers abnormalities in a number of variables, including waist circumference, triglyceride and High Density Lipoprotein (HDL) levels, blood pressure and glucose.

The prevalence of MeS was found to be 20% in a lupus population (N=160) from Spain, compared with an age, sex, ethnically and educationally-matched control group (N=245, p=0.08), while the prevalence of MeS was nearly 4 times that of controls in women aged ≥ 40 years [61]. Higher C3, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP) and triglyceride levels, and lower educational level, HDL and hydroxychloroquine use were all independently associated with MeS in SLE. Cardiovascular disease was twice as prevalent in the SLE group with MeS compared to those without.

In another cross-sectional study, the same group found that, in a multivariate analysis, MeS was significantly associated with aortic stiffness (OR 2.93, CI 1.05-8.93), a predictor of future CVD events, along with disease duration, CRP, male sex and age [62].

The SLICC Registry for Atherosclerosis recently reported that, of nearly 1500 patients followed from inception between the years 2000 and 2009, 16% fulfilled criteria for MeS at baseline [63] defined by the joint interim statement from a number of clinical collaborators and reported in the journal, *Circulation* [64]. Univariate analysis, adjusted for age, sex and ethnicity, revealed a significant association with higher disease activity (SLEDAI-2K), corticosteroid use and renal disease, while antimalarial use was associated with a lower prevalence of MeS. On multivariate regression analysis, corticosteroid use (higher daily average prednisolone use; OR 1.02, CI 1.00 -1.03), older age at diagnosis (OR 1.04, CI 1.03 – 1.06), Korean (OR 6.33, CI 3.68 – 10.86)

and Hispanic (OR 6.2, CI 3.78 – 10.12) ethnicity, active renal disease (OR 1.79, CI 1.14 – 2.8) and the use of immunosuppressive medication (OR 1.81, CI 1.18 – 2.78) were independently predictive of MeS. Corticosteroid and immunosuppressant use may be surrogate markers of disease activity and severity, therefore negating the effect of disease activity in the multivariate analysis; however, given the established knowledge on the effects of corticosteroids on BMI, lipid and glucose levels and blood pressure, it is important to consider corticosteroids' role in predisposing patients to MeS, and thereby increasing risk for atherosclerosis.

Chung et al. explored the factors associated with Insulin Resistance (IR) in Rheumatoid Arthritis (RA) and SLE in the absence of previous CVD [65]. Only BMI was independently predictive of IR (as measured by the homeostasis model assessment (HOMA) index) in SLE, compared with IL-6 and TNF α in RA, suggesting different mechanisms lead to IR in these two rheumatic diseases. The extent of coronary calcification correlated significantly with the HOMA index in the RA group only. Stein's group also examined the role of free fatty acids (FFAs) in IR, in a cross-sectional study comparing 156 SLE patients with 90 controls in the absence of a history of CVD events [66]. The authors found that FFAs were higher in SLE patients, particularly in those with elevated BMI and MeS, and that FFA elevation was associated with insulin resistance (HOMA index) and endothelial activation, as correlated with E-selectin and intercellular adhesion molecule 1 (ICAM-1), but not with systemic inflammation (IL-6 and TNF α).

Taken together, these findings indicate that different mechanisms lead to both IR and atherosclerosis in RA and SLE, and that in MeS, FFAs may be an important component in the pathogenesis of atherosclerosis in lupus.

Homocysteine

Hyperhomocysteinemia is associated with an increase in atherosclerosis-related disease in the general population [67]. The precise mechanisms by which homocysteine is arteriopathic have yet to be defined but are believed to include the induction of endothelial dysfunction (including increased expression of vascular cell adhesion molecule 1 (VCAM-1) and decreased production of endothelial Nitric Oxide (NO)), the promotion of reactive oxygen species production, vascular smooth muscle cell proliferation, the oxidation of low density lipoprotein (LDL) and endothelial cell apoptosis through Fas-mediated pathways [68,69].

The Hopkins Lupus Cohort reported that baseline homocysteine was an independent risk factor for stroke (OR 2.33, CI 1.04-5.75), despite only 51 (15%) patients having levels greater than the upper limit of normal (14.1 μ mol/L) for the investigating laboratory [70]. No association with arterial events was found for folate or vitamin B 12 levels.

As noted above [47], homocysteine concentration is an independent predictor of carotid plaque progression in SLE. In their study, Roman et al. [46] found that only 17 patients (10.7%) had homocysteine levels greater than their laboratory's upper limit of normal (≥ 12 μ mol/L), but that the highest tertile (≥ 7.9 μ mol/L) had the greatest rate of plaque progression at 56.1% compared with 16.2% of those in the lowest tertile. This finding is important as it suggests that homocysteine levels considered normal in the general population, may actually be toxic to the lupus vasculature already predisposed to dysfunction.

Asymmetric dimethylarginine (ADMA) inhibits NO synthase, an essential enzyme in the production of NO, while endothelial-derived NO is an essential mediator of healthy vascular tone with anti-

atherogenic properties [71]. ADMA is predictive of CVD in the general population [72]. Homocysteine increases the synthesis of ADMA and inhibits enzymatic metabolism of ADMA [73]. Perna et al. found that both homocysteine and ADMA were independent predictors of arterial stiffening in 125 SLE patients (correlation coefficient of 0.6 for both), but that levels were not associated with carotid plaque [74].

More recently, a Spanish study found homocysteine to be an independent predictor of CIMT progression over 2 years in 101 SLE patients [75], while coronary artery calcification was associated with homocysteine concentration in 152 lupus patients [76].

Homocysteine, therefore, appears to be a risk factor for sub-clinical atherosclerosis in SLE, and its role as a predictor of AVE requires further study.

Lupus-Specific Factors Associated with Atherosclerosis in SLE

Autoantibodies including antiphospholipid antibodies

SLE is a disease characterized by an increase in circulating immune complexes and antibodies to self-nuclear antigens.

Roman et al. examined correlates of carotid plaque in SLE and found that, in univariate analysis, anti-ribonuclear protein (anti-RNP), anti-Smith (anti-Sm) and anti-cardiolipin antibodies were significantly less prevalent in those with plaque. On regression analysis, however, only anti-Sm antibody remained a significant protective factor against plaque (OR 0.11, CI 0.01-0.98) [46]. Perna et al., from the same institution, reported that the absence of both anti-Sm and anti-RNP antibodies were independently predictive of arterial stiffening, a subclinical marker of vascular disease [74]. Paradoxically, anti-Sm and anti-RNP antibodies have been shown to be associated with elevated interferon- α (IFN α), a cytokine linked to disease severity and endothelial dysfunction in SLE [77], while the Hopkins group found that ADMA ('Homocysteine' above) was positively associated with anti-Sm, anti-RNP, anti-dsDNA, low C4 and coronary calcification [78]. Anti-dsDNA antibody was also found to be an independent predictor of AVE in the Hopkins' cohort [16].

Anti-dsDNA antibody is a marker of disease activity and is associated with lupus nephritis. The associations with atherosclerosis may be reflective of disease severity and activity over time. However, the reports on anti-RNP and anti-Sm antibody are contradictory. Anti-RNP antibody is present in 25 to 47% of SLE patients, and is associated with Raynaud's phenomenon and mild renal involvement. On the contrary, anti-Sm antibody is present in 5 to 30% of patients and is associated with a more severe and active phenotype of lupus nephritis [79]. A degree of protection or harm may be conveyed upon the patient depending on specific attributes of the lupus phenotype and/or genotype. Further prospective, longitudinal studies are required to ascertain the precise role of these antibodies in atherosclerosis of lupus.

Anti-endothelial cell antibodies have a reported prevalence of 15 to 88% in SLE, however their precise role in the development of atherosclerosis is undetermined [80]. Studies in lupus-associated vasculitis have shown their binding stimulates EC activation with up-regulation of ICAM-1, VCAM-1 and E-selectin, IL-1 and IL-6 secretion, pro-coagulant tissue factor production and EC apoptosis.

High density lipoprotein has an important anti-atherogenic role and a diminished HDL level is a risk factor for CVD. Its cardioprotective function arises from a number of roles including in reverse cholesterol transport and in preventing oxidation of LDL through the major

protein component of HDL, apolipoprotein AI (Apo AI) [81]. O'Neill et al. found that levels of anti-HDL and anti-Apo AI antibodies were significantly higher in SLE patients than controls and that patient with persistently active lupus have higher anti-Apo AI levels than patients with quiescent disease [82]. Therefore, disease activity in SLE may partially account for the increased risk of CVD through negating the anti-atherogenic effect of HDL and Apo AI.

The antiphospholipid antibodies (aPL) comprise the lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti- β 2 glycoprotein I (anti- β 2GPI) antibodies, and data from the Hopkins Lupus Cohort suggests that aPL are present in over 70% of SLE patients [83]. While aPL have been shown to up-regulate EC adhesion molecules and increase leukocyte adhesion to ECs, clinical studies offer conflicting evidence regarding the association of aPL and atherosclerosis [84].

Complement

The main function of complement is the recognition and elimination of pathogens, with important roles in immune complex clearance and removal of apoptotic debris. In SLE, complement is both activated and consumed, reflected in decreased C3 and C4 levels, but may, paradoxically, be deficient which would contribute to the development of autoimmunity through accumulation of immune complexes and autoantigens from apoptotic debris, driving autoantibody production [85].

The activation of complement may have a role to play in the formation of atheroma through activation of the endothelium and directing circulating leukocytes to sites of inflammation [86]. Modified lipoproteins have been shown to activate the alternative and classical complement pathways by binding CRP *in vitro* [87] while in the general population, elevated C3 has been shown to be an independent predictor of CAD in symptomatic patients and correlates with markers of the metabolic syndrome [88].

In a murine model of lupus with a pro-atherosclerosis phenotype (Sle16.Ldlr^{-/-}), circulating C3 was significantly reduced compared to Ldlr^{-/-} controls, C3 deposition in arterial lesions was reduced and apoptotic cell numbers were increased in plaques, suggesting that complement deficiency in lupus contributes to accelerated atherosclerosis through impaired clearance of apoptotic debris [89].

An increase in C3 has been shown to be predictive of CIMT progression over 2 years, along with disease duration and homocysteine [75]. Data from the Hopkins' Cohort have also shown a link between higher C3 levels and carotid plaque, with an OR of 1.9 (CI 1.0 - 3.7; p=0.05) for a C3 above the upper limit of normal (>120 mg/dL) [20]. Manger and colleagues identified a significant association between the presence of CAC and an increase in C3 [31].

Vascular stiffness, as quantified by Pulse Wave Velocity analysis (PWV), is predictive of future vascular events in the general population. Increasing values of PWV in 124 pre-menopausal lupus patients were predicted by increasing C3 levels, the presence of carotid plaque, anti-dsDNA antibodies and non-use of hydroxychloroquine [90].

Disease activity

Disease activity in SLE has been shown to be an independent predictor of organ damage and mortality [91,92]. The available evidence suggests that it is a lupus-specific risk factor for atherosclerosis.

The UTLC found that disease activity, as measured by the SLE Disease Activity Index 2000 (SLEDAI-2K), was greater at inception in those who later developed AVE (11.7 \pm 9.5) than in those without

AVE (8.6 ± 6.9 ; $p=0.07$), while the adjusted mean SLEDAI (AMS), an average of disease activity over the years since the diagnosis of lupus, was similar between the two groups [9]. The authors also found that those with a history of an AVE were significantly older at the time of diagnosis than those without a CVD history, and were more likely to be smokers. This would suggest that the inflammatory milieu at the onset of disease has a greater propensity for arterial damage in older vasculature with a malevolent environmental stimulus. Organ damage (as per the SDI, and excluding damage from atherosclerosis) was greater in those with an AVE (1.7 ± 2.0 vs. 0.9 ± 1.2 ; $p=0.01$), implying that disease severity is a component of atherosclerosis in SLE. More recently we have reported that disease activity (HR 1.11, CI 1.04-1.17) was independently predictive of CAD, along with age, in a study examining the effect of hormone replacement therapy on CAD in post-menopausal lupus patients [93].

Steiman et al. reported that the incidence of CAD in patients with serologically active but clinically quiescent disease over 10 years was 1.8% compared with 7.3% in a lupus control group [94]. Disease activity, as measured by the AMS, over 10 years of follow-up was lower in the clinically quiescent cohort (2.54 ± 0.98) compared with the lupus control group (5.05 ± 5.37). These findings again suggest the importance of active disease in the pathogenesis of atherosclerosis.

Magder and Petri report that recent disease activity, recent presence of anti-dsDNA and a history of lupus anticoagulant are independent predictors of CVD events [16], while disease duration is not a risk factor, as has been found in other studies [15,56].

Inflammatory Risk Factors

CRP

The LUMINA cohort found that elevated CRP was independently predictive of future CVD events in a multi-ethnic cohort (OR 3.36, CI 1.26-8.93), along with the presence of any anti-phospholipid antibody (OR 4.72, CI 1.67-13.16), smoking (OR 3.73, CI 1.39-10.00) and older age (OR 1.075, CI 1.04-1.11) [21]. The independent association of high CRP (OR 2.63, CI 1.17-5.91 for CRP in the highest tertile) with CVD events, along with baseline damage index score (SDI; OR 1.28, CI 1.09-1.50) was later confirmed in this cohort [95]. As in the general population, an elevated CRP is indicative of a systemic inflammatory process and is a risk for accelerated atherosclerosis in SLE.

Pro-inflammatory HDL

Pro-inflammatory HDL cholesterol (piHDL) refers to a dysfunctional component of the HDL lipid fraction with impaired ability to prevent oxidation of LDL [96]. Increased oxidative stress may be responsible for the formation of piHDL [97].

McMahon et al., found that SLE patients had a 19-times greater risk of having piHDL than healthy controls while patients with carotid plaque had significantly higher piHDL levels than those without plaque [96]. Almost 50% of SLE patients had piHDL detected. Pro-inflammatory HDL was independently predictive of plaque (OR 16.1, CI 4.3-59.6) and CIMT (OR 2.5, CI 1.1-5.4).

The same research group also reported that low levels of physical activity, a risk factor for CVD in the general population, were associated with piHDL (OR 2.02, CI 1.1-3.9), controlling for disease activity and organ damage (SDI), and that greater levels of physical activity predicted lower CIMT and lower plaque numbers [98].

Oxidized LDL (oxLDL) is an important component of early atherosclerosis. It is a chemoattractant for monocytes, enhances

monocyte-EC adhesion, is cytotoxic to EC and stimulates T-cell activation in early atheromata. Its uptake by intimal macrophages leads to the formation of foam cells, a pivotal constituent of early plaque [99]. The levels of antibodies to oxLDL in SLE have been shown to correspond to disease activity and complement components [100], while elevated levels of oxLDL/ β 2GPI complexes and IgG anti-oxLDL/ β 2GPI antibodies are associated with increased IMT in SLE [101].

Role of Medications

Corticosteroids

Corticosteroids were introduced to clinical care in the 1950s and have contributed to the increased survival of lupus patients over the decades. However, an increasing volume of evidence implicates their role in the acceleration of atherosclerosis, which may partly be due to their propensity to induce dyslipidemia, hypertension [55], obesity and insulin resistance [102,103]. In contrast, as atherosclerosis has been shown to be an inflammatory process, corticosteroids might prevent atheroma formation through its anti-inflammatory properties.

Doria et al. reported that the cumulative dose of prednisone, along with age, was an independent predictor of carotid plaque (OR 1.09, CI 1.03-1.16) in 78 Italian patients with no prior history of CVD events [104]. In contrast, Roman et al. found that, among SLE patients, those with carotid plaque had a significantly lower daily dose of corticosteroid averaged over a 5 year period compared with those without plaque ($p=0.002$) [46].

While corticosteroid exposure and high cumulative doses may be reflective of disease activity, which itself may contribute to atherosclerotic risk, recent evidence from the Hopkins Lupus Cohort, adjusting for mean disease activity over time, shows that current corticosteroid use, along with age, is a strong predictor of organ damage accrual in lupus [105].

Outcome studies from the UTLC have also examined the effect of corticosteroids on damage accrual as quantified by the SDI, an instrument used to identify irreversible organ damage in 12 organ systems [106]. Definite corticosteroid-related damage was attributed to the ocular (cataract or retinal change) and musculoskeletal systems (muscle atrophy/weakness, osteoporosis, osteonecrosis), while possible corticosteroid-related damage was assigned to CVD (angina, coronary artery bypass surgery, myocardial infarction), diabetes and the neuropsychiatric component (stroke) [7]. Of the 73 patients in the inception cohort followed for at least 15 years, 31% of those with documented organ damage had either cardiovascular disease including stroke and/or diabetes.

In a separate study from the UTLC, corticosteroid use, including duration of use and cumulative dose, was related to AVE on univariate analysis, however the significance was not maintained on multivariate analysis [9].

In the Steiman et al. study, patients with 'serologically active but clinically quiescent' SLE had significantly less organ damage accrual over 10 years compared with a lupus control group [94]. Corticosteroid use and damage "possibly attributable to corticosteroid use" (as defined above) was greater in SLE controls.

Bruce et al. has shown that, in the early years after diagnosis, cumulative corticosteroid dose is associated with a sustained elevation in total serum cholesterol, which in turn is predictive of future CAD-related events [54].

Magder and Petri determined that a current corticosteroid dose \geq

20 mg was independently predictive of CVD events, with a rate ratio of 2.54 (CI 1.44-4.48) and was more strongly associated with CVE risk than cumulative past dose [16]. This suggests an acute effect on the arterial vasculature in SLE.

The available evidence indicates an undefined role for corticosteroids in atherosclerosis in SLE. It may be that corticosteroids abrogate the level of inflammation present in the vasculature of SLE patients, but that its effects on serum cholesterol, body mass index and insulin resistance nullify the anti-inflammatory component and eventually tip the balance in favour of atheroma formation.

Antimalarial medication

Antimalarial (AM) use has been shown to be associated with a 42% reduction in mortality risk in SLE [8] and to slow progression to permanent organ damage, perhaps through its anti-inflammatory, anti-thrombotic, anti-hyperglycemic and anti-hypercholesterolemic effects [107]. However, as AM use tends to be associated with a less severe lupus phenotype, studies examining its role in disease outcomes are limited by the possibility of confounding by indication. This was addressed by the UTLC where a nested case-control study was conducted matching SLE cases (N=54) with a history of thrombovascular (TE) events (both venous and arterial) to those without (N=108) according to disease activity, duration of follow-up and calendar year of inception into the Clinic [108]. Multivariate regression analysis revealed that use of antimalarial drugs was associated with a 68% reduction (OR 0.32, CI 0.14-0.74) in the risk of TEs. While these results highlight the case for antimalarials' anti-thrombotic effect, they do not inform as to their anti-atherosclerosis capability.

The CVD-protective effect of hydroxychloroquine may be through its ability to lower serum cholesterol [109] and to reduce the incidence of disease flares [110]. The UTLC has shown that AM use, despite concomitant corticosteroid prescription, is associated with significantly lower total cholesterol, LDL and VLDL cholesterol [111].

Hydroxychloroquine use is independently predictive of less organ damage accrual over a mean follow-up of 46 months as seen in an Israeli cohort of 151 patients, with significantly longer duration of damage-free survival compared with non-hydroxychloroquine use ($p < 0.0001$) [112].

Vascular stiffness has been shown to be associated with the absence of hydroxychloroquine use in premenopausal lupus patients [91]. Thrombotic events (arterial and venous) were significantly lower in hydroxychloroquine users, while 15-year survival rates were greater in hydroxychloroquine users than non-users (0.95 vs. 0.68, $p < 0.001$) [113].

Those with carotid plaque amongst 197 SLE patients were found to have significantly less use of hydroxychloroquine (63%) compared to those with no plaque (82.3%, $p = 0.003$) [46]. Despite the loss of this association on logistic regression analysis, it does suggest that antimalarial use may have protective effects against the development of atherosclerosis, either through an anti-inflammatory pathway or through early suppression of disease activity, or both.

The LUMINA group has shown that reduced disease activity after treatment with hydroxychloroquine was significantly correlated with reduced INF- α levels [114], a cytokine important in the pathogenesis of atherosclerosis [115].

It is becoming increasingly apparent that AM treatment in SLE has atherosclerotic-protective effects, and its corticosteroid-sparing properties may be equally important in this regard. The UTLC has addressed the issue of confounding by indication in terms of thrombovascular risk, but that of AVE requires on-going investigation.

HMG CoA reductase inhibitors (Statins)

As a sustained elevation in total cholesterol in the early stages of SLE is predictive of subsequent CAD-related events [54], tight control of lipid levels may improve survival and prevent atherosclerosis-related morbidity.

Statins lower LDL cholesterol and are used in the primary and secondary prevention of atherosclerotic vascular disease [116]. However, their beneficial effect in atherosclerosis treatment may be pleiotropic, including an anti-inflammatory component [117] and the down-regulation of endothelial cell activation [118].

A small randomized placebo-controlled study looking at the effect of atorvastatin (40 mg) on coronary artery calcification and myocardial perfusion in SLE found that, in the group randomized to atorvastatin, calcium score and coronary plaque volume remained static after 1 year of treatment, while these same variables progressed significantly in the placebo arm [119]. Baseline CRP, total cholesterol and LDL were significantly decreased after 1 year of treatment, compared to the placebo arm, suggesting a mechanism of action other than lipid-lowering.

A much larger placebo-controlled trial of atorvastatin (40 mg) from the Hopkins Lupus Cohort, conducted over 2 years found no significant difference between the two groups in progression of CAC, CIMT, carotid plaque, disease activity (SLEDAI), markers of inflammation (high sensitivity CRP and IL-6), homocysteine and markers of endothelial activation/dysfunction (soluble ICAM-1, VCAM-1 and P-selectin) [120]. The study period may, however, have been of insufficient duration to enable quantifiable improvements in surrogate measures of atherosclerosis to be seen. Extension of this study over a greater time period to examine the effect on CVD events would be of interest.

Conclusions

Atherosclerosis is accelerated in SLE however the precise mechanisms remain elusive. Based on the existing evidence, however, the pathogenesis is likely influenced by the interaction of a multitude of variables, including traditional CVD risk factors (particularly dyslipidemia, male sex and homocysteine), lupus-specific factors (including disease activity and age at diagnosis), lupus-directed therapies such as corticosteroids and antimalarial medication, ethnicity and systemic inflammation.

The identification of patients at greatest risk of future AVE at the earliest time-point after diagnosis remains a challenge for rheumatologists; however, this is an important component in the holistic management of SLE. While imaging studies in subclinical atherosclerosis have informed our current knowledge of future risk of AVE, their precise role in clinical practice remains undefined.

Consideration to the construction of risk models with high positive predictive values (PPV) for future AVE that are both clinically practical and reproducible, is relevant. As no single variable conveys the entirety of risk for future AVE in SLE, such models would ideally be drawn from readily available demographic, laboratory and clinical data. It remains to be elucidated if the inclusion of a surrogate of atherosclerosis based on a particular imaging modality would increase the PPV of such models. Research in this regard is on-going.

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