RHEUMATOLOGY

Rheumatology 2011;50:2071–2079
doi:10.1093/rheumatology/ker285
Advance Access publication 28 August 2011

Original article

Predictors of progression in atherosclerosis over 2 years in systemic lupus erythematosus

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Abstract

Objectives. Cardiovascular disease remains the major cause of death in SLE. We assessed the degree to which cardiovascular risk factors (CVRFs) and disease activity were associated with 2-year changes in measures of subclinical atherosclerosis.

Methods. One hundred and eighty-seven SLE patients participating in a placebo-controlled trial of atorvastatin underwent multi-detector CT [for coronary artery calcium (CAC)] and carotid duplex [for carotid intima–media thickness (IMT) and carotid plaque] twice, 2 years apart. During the 2 years, patients were assessed every 3 months for CVRF. Both groups were combined for analysis, as atorvastatin did not differ from placebo in preventing progression of coronary calcium. We examined the correlation between these clinical measures and progression of CAC, IMT and plaque during the follow-up period.

Results. In an analysis adjusting for age, gender and ethnicity, CAC progression was positively associated with total serum cholesterol measured over the 2-year period ($P = 0.04$) and smoking ($P = 0.003$). Carotid IMT progression was associated with systolic BP ($P = 0.003$), high-sensitivity CRP (hsCRP) ($P = 0.013$) and white blood cell (WBC) count ($P = 0.029$). Carotid plaque progression, defined as patients without carotid plaque at baseline with subsequent development of plaque at follow-up, was associated with systolic BP ($P = 0.003$), WBC count ($P = 0.02$), physician's global assessment ($P = 0.05$), blood lymphocyte count ($P = 0.048$), urine protein ($P = 0.017$) and duration of SLE ($P = 0.019$).

Conclusion. Our data did not provide evidence of an association between measures of SLE disease activity (SLEDAI, anti-dsDNA, anti-phospholipid and treatment) and progression of subclinical atherosclerosis. Age and hypertension were associated with the progression of carotid IMT and plaque. Age, smoking and cholesterol were associated with progression of CAC.

Key words: Systemic lupus erythematosus, Helical computed tomography, Coronary artery calcium, Carotid intima–media thickness, Carotid plaque, Inflammation, Atherosclerosis, Carotid duplex, Coronary artery disease, Statins.

CLINICAL SCIENCE

Introduction

In developed countries, atherosclerosis is a major cause of morbidity and mortality in SLE [1, 2]. In 1976 Urowitz *et al.* [3] identified a bimodal mortality curve in SLE, with early deaths due to active disease and infection, and late deaths (patients aged >40 years) due to cardiovascular disease. Recently Hak *et al*. [4] estimated that cardiovascular risk was increased by >2-fold in women with SLE. However, this study was based on only 20 SLE events. In contrast, female SLE patients between 35 and 44 years of age in Pittsburgh were 50 times more likely to have a myocardial infarction than age-specific rates in Framingham offspring study controls, based on 11 cardiovascular events in SLE patients in this age group [5].

Traditional cardiovascular risk factors (CVRFs), including hyperlipidaemia, hypertension, obesity and smoking have been studied in SLE cohorts [6]. Traditional CVRFs do not explain the entire risk of cardiovascular disease [7], suggesting that, as in the general population, inflammation or other factors play a role [8].

Non-invasive methods of detecting subclinical atherosclerosis, including multi-detector CT and carotid duplex,

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Submitted 7 February 2011; revised version accepted 11 July 2011.

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are used to detect subclinical atherosclerosis in coronary and carotid arteries. Subclinical measures of atherosclerosis, including coronary artery calcium (CAC) scores, are predictive of future cardiovascular events [9–13]. Measurement of CAC has been suggested as a potential means for non-invasive assessment of subclinical atherosclerosis in the general population to determine aggressiveness of preventive strategies [14, 15].

Carotid duplex ultrasonography (US) can ascertain both the degree of plaque in the carotid arteries and the intima–media thickness (IMT) and predicts the risk for cardiovascular events [16]. Carotid atherosclerosis has been widely studied in SLE using duplex US [17, 18]. Several cardiovascular trials in the general population have used carotid US as a surrogate for cardiovascular events [19, 20].

Past studies have determined several predictors of subclinical atherosclerosis in SLE. CAC is associated with older age, smoking, male sex, reduced renal function, IL-6 and monocyte chemoattractant protein-1 (MCP-1) [21–25]. Our previous work has also shown age, obesity and diabetes mellitus to be independently associated with CAC [26]. Associates of carotid plaque in SLE have included age, higher homocysteine, higher systolic blood pressure (BP), high high-density lipoprotein (HDL) cholesterol, diabetes mellitus, smoking and serum creatinine >1.3 mg/dl [27–29]. Carotid IMT associates in SLE have included older age, higher SLICC damage scores and cumulative prednisone dosage [29–31].

Recently several groups of investigators have measured changes in subclinical atherosclerosis among SLE patients and explored the association between progression and traditional and SLE-related risk factors. Some recent data suggest important determinants of progression of atherosclerosis (as measured by carotid IMT and carotid plaque) in women with SLE [27, 32–34]. These include higher serum C3 levels, immunosuppressant use at baseline, higher serum creatinine levels, age and baseline homocysteine concentration [27, 32]. Rua-Figueroa *et al*. [33], in their 2-year study of 101 SLE patients, found age at diagnosis, C3, C5a and homocysteine to be risk factors for carotid IMT progression.

de Leeuw *et al*. [34], in their study of 74 SLE and 74 controls, showed that age and disease duration were independently related to carotid IMT. These past studies did not measure changes in coronary calcium score, and only considered risk factors measured at baseline. We hypothesize that clinical measures made during the follow-up period would be more directly related to changes in atherosclerosis than those measured only at baseline.

In the general population, Kronmal *et al*. [35] examined risk factors for the incidence and progression of CAC in asymptomatic subjects from four racial/ethnic groups. The most important traditional risk factors associated with both incidence and progression of CAC were older age, diabetes mellitus, higher BMI, white race, male gender, hypertension and family history of myocardial infarction. In the studies of diabetic patients, blood pressure, central adiposity and urine albumin-to-creatinine ratio have been shown to be predictors of CAC progression [36–38].

The aim of our study was to determine the rate and predictors of progression of subclinical atherosclerosis in SLE patients >2 years, including the first study of progression of coronary calcium in SLE. Patients were recruited from a randomized clinical trial of atorvastatin *vs* placebo to investigate whether statin therapy for 2 years would reduce subclinical measures of atherosclerosis [39]. Two hundred patients were randomly assigned to atorvastatin (40 mg) *vs* matching placebo. Statin use had no benefit in progression, so the two groups were combined. Therefore, to extend previous work in this field, we measured changes in three measures of subclinical atherosclerosis (coronary calcium, IMT and carotid plaque) and explored the association between clinical measures made during follow-up and changes in these measures of subclinical atherosclerosis. Patients in both groups were combined in our analysis.

Methods

The study sample consisted of members of the Hopkins Lupus Cohort who had participated in a randomized double-blind placebo-controlled trial of atorvastatin (40 mg) *vs* matching placebo with 100 patients getting atorvastatin and 100 getting placebos [26]. Two hundred patients with SLE were enrolled in this trial, with follow-up data available on 187. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave informed consent. Patients with a history of an atherosclerotic event (such as angina or myocardial infarction), low-density lipoprotein (LDL) cholesterol level of >190 mg/dl or triglyceride level of >500 mg/dl were excluded.

As part of the Hopkins Lupus Cohort Study, all patients were seen quarterly for assessment of SLE disease activity [by the physician's global assessment, on a 0–3 visual analogue, and the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI] [40, 41] and laboratory tests (complete blood count, ESR, serum creatinine, cholesterol, urinalysis, urine protein/creatinine ratio, C3, C4 and CVRFs, including total cholesterol, homocysteine, lipoprotein(a) and fibrinogen). Anti-dsDNA, anti-cardiolipin and LA (by DRVVT) were tested quarterly. Hypertension was defined as systolic blood pressure $\geqslant 140$ mmHg and diastolic blood pressure $\geqslant 90$ mmHg, or hypertension under treatment.

At baseline, CAC was assessed by multi-detector CT. Carotid IMT and carotid plaque were assessed by carotid duplex US. Tests were repeated at the end of 2 years. Both treatment groups (those on statins and those on placebo) were combined for the analysis of progression.

Image acquisition and evaluation

Multi-detector CT

Coronary artery calcification was assessed by multi-detector CT with a Siemens Volume Zoom Scanner (Siemens Medical Solutions, Malvern, PA, USA) using a

2.5 mm collimation and a slice width of 3 mm. Both scans were done on the same machine. Data were reloaded into a Siemens Leonardo workstation using the Siemens calcium scoring software. Coronary artery calcification was quantified using a standard scoring system, available as part of the scanner software package [42]. Coronary artery calcification scores were calculated using Agatston scoring.

Carotid duplex

High-resolution B-mode US was performed at baseline and 24 months to image the right and left common carotid arteries using a single ultrasound machine (Philips Medical Systems Sonos 5500) with a linear array 8-MHz scan head with standardized image settings, including resolution mode, depth of field, gain and transmit focus. Digital imaging and communications in medicine (DICOM) images from a diastolic frame of the cine-loop recording were electronically stored and transferred via optical disk to an off-line work station for analysis. Carotid IMT was measured between the lumen–intima and media–adventitia interfaces of the far wall of the common carotid artery (the 1-cm segment proximal to the bifurcation) by a single reader using an automated edge detection system. The mean IMT of this 1-cm segment was measured on two separate images of the left and the right common carotid artery at the peak of the R wave on a simultaneous ECG tracing. The mean of these four measurements was used as the IMT. This location was chosen because of its demonstrated reproducibility compared with measurements of carotid IMT at other sites [43, 44]. Each US examination was performed as an independent study, without knowledge of the previous IMT results. Both patients and providers were blinded to the IMT results until the 2-year follow-up examination was completed. Carotid plaque was defined as focal protrusion into the lumen with a thickness at least 50% greater than the surrounding IMT [27, 32]. Both scans were done on same machine and read by one person blinded to treatment assignment.

Statistical analysis

We used an area under the curve (AUC) based on the trapezoidal method to calculate cumulative exposure during the 2 years between the assessments of subclinical atherosclerosis. This is equivalent to taking a weighted average of all the observations during the two periods, giving less weight to observations that were close in time to other observations. Then, to quantify the association between these cumulative exposures and changes in subclinical atherosclerosis measures, we calculated Spearman's correlation coefficients (R) after controlling for (i.e. partialling out) age, sex and race. Those variables with statistically significant ($P < 0.05$) partial Spearman's correlation coefficients were then rank transformed and included in multivariable regression models.

We used Spearman's correlation coefficients and rank-transformed data because they are less affected by outliers. However, they do not take full advantage of all the quantitative information. Therefore, in addition, we also calculated Pearson's correlation coefficients (R) on log-transformed data, after controlling for age.

Carotid plaque was analysed as a binary variable using a logistic regression model, controlling for age. In this analysis we included only those patients without carotid plaque at baseline, as only they were at risk for progression, and assessed the association between various risk factors and incident carotid plaque at follow-up. For quantitative exposures, we report the odds ratios per 1 S.D. difference in degree of exposure.

Results

Patient characteristics

Data were obtained on 187 SLE subjects (92% females). The patients were 61% Caucasian, 34% African-American, 2% Asian, 2% Hispanic and 1% of other ethnicity. The mean (S.D.) age was 44.3 (11.4) years. Ninety-five per cent had four or more ACR classification criteria for SLE, whereas 5% had three. Cumulative SLE clinical manifestations included malar rash 63%, discoid rash 23%, photosensitivity 60%, oral ulcers 54%, arthritis 80%, serositis 50%, renal disorder 40%, neurological disorder 9%, immunological disorder 75%, haematologic 84% (leucopenia 50%, thrombocytopenia 20%, haemolytic anaemia 7% and lymphocytopenia 44%) and ANA positivity 97%.

Thirty-four per cent had a cholesterol >200 mg/dl, 8% had a cholesterol >240 mg/dl, and 10% had elevated triglycerides (>500 mg/dl). Forty-eight per cent had hypertension, 5% had diabetes mellitus and 40% had ever smoked (17% were current smokers).

Prevalence of subclinical atherosclerosis at baseline

At baseline, CAC was found in 43%, with scores ranging from 0.1 to 3885.3. A CAC score >100 was found in 9%. At baseline, the mean (S.D.) carotid IMT was 0.57 (0.10) mm, and of the 183 patients with baseline assessment of carotid plaque (defined as focal protrusion into the lumen with a thickness at least 50% greater than the surrounding IMT), was found in 33 (18%).

Changes in measures of subclinical atherosclerosis over the 2-year follow-up

The mean (S.D.) for the progression of log-transformed coronary artery calcification change was 0.11 (1.1). To determine the number with increases and decreases, an increase or decrease was defined if the score changed by >10 agatston units (AU). Based on this cutoff, 143 (76%) stayed the same, 6 (3%) had a decline and 38 (20%) had an increase in CAC score.

The mean (S.D.) change in IMT was an increase of 0.084 (0.105). Of the 33 with carotid plaque at baseline, all were positive for carotid plaque at 2-year follow-up. Of the 150 patients without carotid plaque at baseline, 36 (24%) developed carotid plaque at follow-up.

Association between traditional risk factors and progression

Table 1 shows the Spearman's correlation coefficients to quantify the degree of association between traditional CVRFs experienced during the follow-up and progression of CAC and IMT and carotid plaque, adjusting for age, race and sex. Age was associated with progression of all three measures of subclinical atherosclerosis, namely CAC ($R = 0.26$, $P = 0.0003$), carotid IMT ($R = 0.26$, $P = 0.0005$) and carotid plaque (OR = 2.4, $P = 0.0003$). Total serum cholesterol measured during the follow-up period was associated with the progression of CAC ($R = 0.15$, $P = 0.043$), but not with carotid IMT ($R = 0.10$, $P = 0.17$) or carotid plaque (OR = 1.1, $P = 0.67$). High-sensitivity CRP (hs-CRP) was negatively associated with progression of CAC (R = −0.23, $P = 0.0017$), but positively associated with carotid IMT ($R = 0.18$, $P = 0.013$). Interestingly, current smoking was associated with progression of CAC ($R = 0.22$, $P = 0.0026$) and carotid IMT ($R = 0.14$, $P = 0.074$), but not with progression of carotid plaque (OR = 1.7, $P = 0.54$), although the OR was >1. Systolic blood pressure was associated with progression of carotid IMT ($P = 0.0031$) and carotid plaque ($P = 0.0027$), but not with CAC progression. A history of hypertension was strongly associated with the progression of carotid plaque (OR = 6.8, $P < 0.0001$), but not carotid IMT ($P = 0.21$) or CAC progression ($P > 0.87$).

Association between SLE-related risk factors and progression

Table 2 shows the degree of association between measures of SLE disease activity and changes in markers of atherosclerosis, adjusting for age, race and sex. There was no association between the SELENA-SLEDAI measured during the follow-up period and 2-year progression. However, the physician's global assessment was associated with carotid plaque progression (OR = 1.6, $P = 0.053$). There was some evidence that higher C3 was associated with progression of carotid IMT ($R = 0.14$, $P = 0.070$), but that lower C3 was associated with progression of CAC ($R = -0.14$, $P = 0.090$). Neither the LA (by DRVVT) nor the anti-dsDNA were associated with progression. Prednisone and HCQ had no effect on progression either (Table 2). Those with SLE for a longer duration had greater odds of carotid plaque progression (OR = 2.3, $P = 0.019$). Consistent with this, those with a later diagnosis of SLE had a lower rate of progression (OR = 0.4, $P = 0.018$).

Association between laboratory measurements during the follow-up and progression of atherosclerosis

The white blood cell (WBC) count during follow-up ($R = 0.16$, $P = 0.029$) was associated with 2-year progression of carotid IMT and carotid plaque progression (OR = 1.6, $P = 0.020$), but was not associated with CAC progression (Table 3). Lymphocyte count and urine protein were significantly associated with the incidence of carotid plaque.

Additional analyses

The results of the analysis based on the age-adjusted Pearson's correlation coefficients were generally the same as those found with the age-adjusted Spearman's correlation coefficients described above. One exception was

Table 1 Association between exposure to traditional risk factors and 2-year change in subclinical measures of atherosclerosis

Exposure	CAC		Carotid IMT		Carotid plaque	
	R^a	*P*-value	R^a	*P*-value	OR[b] (95% CI)	*P*-value
Traditional risk factors						
Age	0.26	0.0003	0.26	0.0005	2.4 (1.5, 3.9)	0.0003
Cholesterol	0.15	0.043	0.10	0.17	1.1 (0.7, 1.7)	0.67
LDL at baseline	0.05	0.55	0.02	0.80	0.9 (0.6, 1.4)	0.77
hsCRP	−0.23	0.0017	0.18	0.013	1.1 (0.8, 1.6)	0.62
Systolic blood pressure measured during follow-up	0.02	0.75	0.22	0.0031	2.1 (1.3, 3.4)	0.0027
Diastolic blood pressure measured during follow-up	0.04	0.63	0.18	0.013	2.1 (1.3, 3.5)	0.0031
BMI	−0.13	0.077	0.07	0.35	1.4 (0.9, 2.2)	0.11
Current smoking (yes/no)	0.22	0.0026	0.14	0.074	1.7 (0.4, 4.9)	0.54
Past smoking (yes/no)	0.12	0.12	0.02	0.88	1.6 (0.3, 8.7)	0.26
Diabetes mellitus (yes/no)	−0.05	0.54	0.07	0.32	6.3 (0.8, 48.4)	0.076
History of hypertension (yes/no)	0.01	0.87	0.09	0.21	6.8 (2.6, 17.4)	<0.0001
On anti-hypertensives[c]	−0.04	0.62	−0.01	0.94	1.6 (1.2, 2.1)	0.0004
Serum creatinine	−0.05	0.48	0.08	0.31	1.8 (0.6, 5.8)	0.31

[a]Partial Spearman's correlation coefficients, controlling for age, gender and ethnicity. [b]Based on a logistic regression model, controlling for age, gender and ethnicity. All odds ratios are with respect to a 1 S.D. difference in exposure level. [c]Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Table 2 Association between measures of SLE disease activity, serologies and medications made during follow-up and 2-year change in subclinical measures of atherosclerosis

Exposure	CAC		Carotid IMT		Carotid plaque	
	R^a	*P*-value	R^a	*P*-value	OR[b] (95% CI)	*P*-value
Measures of disease activity						
Physician's global assessment	0.01	0.85	0.07	0.35	1.6 (1.0, 2.5)	0.053
SELENA-SLEDAI	−0.03	0.64	−0.03	0.73	1.3 (0.8, 2.0)	0.25
Lupus serologies						
C3 (continuous)	−0.14	0.090	0.14	0.070	1.2 (0.8, 1.9)	0.26
C4 (continuous)	0.09	0.22	0.13	0.089	1.2 (0.8, 1.8)	0.40
Anti-dsDNA+1	−0.07	0.37	0.04	0.63	0.9 (0.6, 1.5)	0.79
LA by DRVVT	−0.01	0.88	0.07	0.35	1.0 (0.6, 1.5)	0.88
Medications						
Prednisone dose	0.12	0.12	0.08	0.26	1.1 (0.7, 1.6)	0.79
HCQ	−0.01	0.84	−0.08	0.28	0.7 (0.5, 1.1)	0.12
Lupus history at baseline						
SLE duration	0.03	0.67	−0.07	0.12	2.3 (1.1, 4.5)	0.019
Age at diagnosis.	−0.03	0.70	0.11	0.13	0.4 (0.2, 0.9)	0.018

[a]Partial Spearman's correlation coefficients, controlling for age, gender and ethnicity. [b]Based on a logistic regression model, controlling for age, gender and ethnicity. The ORs for SLE duration and age at diagnosis are per 10-year difference. All other ORs are with respect to 1 S.D. difference in exposure level.

Table 3 Association between laboratory measurements made during follow-ups and 2-year change in subclinical measures of atherosclerosis

Exposure	CAC		Carotid IMT		Carotid plaque	
	R^a	*P*-value	R^a	*P*-value	OR[b] (95% CI)	*P*-value
Tests						
Haematocrit	−0.03	0.67	0.07	0.32	0.8 (0.5, 1.3)	0.42
WBC count	0.00	0.97	0.16	0.029	1.6 (1.1, 2.4)	0.020
Platelet count	−0.06	0.44	0.10	0.16	1.1 (0.7, 1.7)	0.57
Lymphocyte count	−0.09	0.28	0.11	0.16	1.6 (1.0, 3.9)	0.048
Urine protein	−0.10	0.16	0.09	0.23	1.7 (1.1, 2.6)	0.017
Urine red blood cells	0.03	0.65	0.03	0.68	1.2 (0.8, 1.8)	0.45

[a]Partial Spearman's correlation coefficients, controlling for age, gender and ethnicity. [b]Based on a logistic regression model, controlling for age, gender and ethnicity. All ORs are with respect to 1 S.D. difference in exposure level.

that we found a significantly positive association between diabetes mellitus and change in carotid IMT (Pearson's $R = 0.19$, $P = 0.0086$). Another interesting exception was that we found that C4 was negatively associated with progression of coronary calcium (Pearson's $R = -0.16$, $P = 0.033$), but positively associated with change in carotid IMT (Pearson's $R = 0.19$, $P = 0.012$). The Pearson's analysis also found that progression of carotid IMT was positively associated with the platelet count (Pearson's $R = 0.14$, $P = 0.052$) and lymphocyte count (Pearson's $R = 0.19$, $P = 0.018$).

Multivariable analyses

Age, cholesterol, low high-sensitivity CRP (hsCRP) and current smoking were all predictive of progression of coronary calcium in univariate analyses. When all these variables were put in the same regression model (using ranked data), age, current smoking and low hsCRP remained strongly associated with coronary calcium progression, while the evidence for an association with cholesterol was weakened ($P = 0.076$). Age, high hsCRP, systolic blood pressure and WBC counts were all associated with progression of carotid IMT in univariate analyses. When all were put in the same regression model, age and systolic blood pressure continued to have a strong association with progression, but the evidence for association was weaker for hsCRP ($P = 0.11$) and WBC counts ($P = 0.15$). Age, history of hypertension, SLE duration, WBC count, lymphocyte count and urine protein were associated with the incidence of carotid plaque in

univariate analyses. When all were entered into a multivariable logistic regression, age and history of hypertension remained strongly predictive of incident carotid plaque, and there was still moderate evidence of an association between duration of SLE and incident carotid plaque (OR = 2.8, $P = 0.062$), but there was less evidence for an association with the other variables ($P > 0.13$ for others).

Discussion

The direct connection between SLE and accelerated atherosclerosis has not been clear. In our study, multiple measures of SLE disease activity (except for physician's global assessment, which was associated with progression of carotid plaque), SELENA-SLEDAI or anti-dsDNA did not predict progression of subclinical atherosclerosis as measured by CAC or carotid duplex US. This is in agreement with our previous work on associates of prevalent CAC [26] and carotid atherosclerosis [29]. aPL did not predict progression of any subclinical measure of atherosclerosis in this study. Age was strongly associated with progression of CAC, carotid IMT and carotid plaque in our study. We have previously shown that age, obesity and diabetes mellitus were independently associated with prevalent CAC in our study of 200 SLE patients [26].

Several previous studies [27, 33, 34] reported a positive association between age at diagnosis of SLE and progression of atherosclerosis. However, these studies did not control for age. Age is an important confounder in this analysis because it is strongly related to both progression of atherosclerosis and age of diagnosis in a given sample. When we adjusted for age, we did not observe an association between age at diagnosis and progression of coronary calcium or carotid IMT, and we found a statistically significantly negative relationship between age at diagnosis and risk of incident carotid plaque.

Similarly, previous studies have reported a relationship between SLE duration and progression of atherosclerosis without adjusting for age. When we adjust for age in our study, we did not observe a relationship between SLE duration and progression of coronary calcium or carotid IMT, consistent with one previous study that also adjusted for age [32]. We did, however, observe a significant association between SLE duration and incident carotid plaque, even after adjusting for age.

We and others have previously shown an association of high-serum C3 with prevalent carotid plaque and CAC [22, 29]. High C3 levels are also associated with aortic stiffness in SLE, another predictor of cardiovascular mortality [45]. High C3 levels in the general population show an association with both waist/hip circumference and postprandial lipaemia [46]. Thompson *et al.* [32] have also shown that higher serum C3 levels predict plaque progression. High levels of C3 have been shown in patients with atherosclerosis in the general population [47] and have also been shown to be associated with the risk of myocardial infarction in apparently healthy men [48]. In our study, there was some evidence of an association between high C3 and CAC progression, and also some evidence of an association between low C3 and IMT progression.

Systolic blood pressure did predict the progression of carotid IMT and carotid plaque in our SLE patients. In the general population (the Bogalusa Heart Study), systolic blood pressure and BMI were predictors of carotid IMT progression [49]. In a 3-year follow-up study, carotid IMT progression was significantly correlated with age, hypertension, diabetes mellitus and smoking [50]. Hypertension and age were also very strongly associated with carotid plaque progression in our study. We have also previously shown hypertension to be an independent associate of prevalent carotid plaque [29].

In our univariate analysis, we also found that the WBC count predicted the progression of carotid IMT and carotid plaque. In the general population, Gillum *et al*. [51] showed no significant association between the leucocyte cell count with stroke, whereas Kannel *et al*. [52] and Phillips *et al*. [53] showed that the leucocyte cell count was positively associated with development of cardiovascular disease, including stroke and coronary heart disease (CHD).

Smoking is considered to be an independent risk factor for vascular events in SLE [54]. A past study found that African-American SLE patients with a history of smoking had significantly higher carotid IMT than ones who never smoked [55]. In our study, current smoking was associated with progression of CAC.

In our study, 20% of the patients had an increase in CAC during the 2-year follow-up. Similar increases have been seen in other studies in the general population [56, 57]. Janowitz *et al*. [56] showed a 22% increase in calcified plaque volume among asymptomatic subjects compared with a 48% increase with proven coronary artery disease. Ours is the first study to show progression of coronary artery calcification among SLE patients.

Age was significantly associated with progression of all three measures in our study. The relationship between age and atherosclerosis cannot be over-emphasized. We have previously shown that age also correlates with atherosclerotic manifestations [5]. This study further strengthens this key relationship that must be taken into account in statistical analyses.

Our data suggest that stringent control of hypertension, cholesterol and smoking in SLE should be emphasized. In the general population, nearly three-fourths of adults in the USA with cardiovascular morbidity have poor control rates of systolic hypertension [58]. Others have suggested that SLE, as with diabetes mellitus, should be considered as a CHD-equivalent condition, mandating strict control of traditional CVRFs [59]. In our analysis using Pearson's correlation coefficients, we have also shown diabetes mellitus to be associated with carotid IMT. SLE patients with hyperlipidaemia should continue to be treated with statins and other anti-hyperlipidaemic medications if they meet the National Cholesterol Education Program (NCEP) guideline thresholds for treatment [60].

SLE itself is thought to initiate the atherosclerotic process. Our analysis emphasized the role of traditional risk factors as important predictors of progression of disease. This strongly suggests that control of cholesterol, smoking and hypertension should be priority intervention targets in SLE.

Rheumatology key message

- The study emphasized the role of traditional CVRFs as important predictors of progression of atherosclerosis.

Acknowledgements

The Lupus Atherosclerosis Prevention Study was supported by a grant from the Alliance for Lupus Research, the Arthritis Foundation, the Hopkins Lupus Cohort (NIH AR 43727), and by grant number UL1 RR 025005 from the National Center for Research Resources (NCRR).

Disclosure statement: The authors have declared no conflicts of interest.

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