

ORIGINAL ARTICLE

Prevalence and Correlates of Accelerated Atherosclerosis in Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND

Although systemic lupus erythematosus is associated with premature myocardial infarction, the prevalence of underlying atherosclerosis and its relation to traditional risk factors for cardiovascular disease and lupus-related factors have not been examined in a case-control study.

METHODS

In 197 patients with lupus and 197 matched controls, we performed carotid ultrasonography, echocardiography, and an assessment for risk factors for cardiovascular disease. The patients were also evaluated with respect to their clinical and serologic features, inflammatory mediators, and disease treatment.

RESULTS

The risk factors for cardiovascular disease were similar among patients and controls. Atherosclerosis (carotid plaque) was more prevalent among patients than the controls (37.1 percent vs. 15.2 percent, $P < 0.001$). In multivariate analysis, only older age, the presence of systemic lupus erythematosus (odds ratio, 4.8; 95 percent confidence interval, 2.6 to 8.7), and a higher serum cholesterol level were independently related to the presence of plaque. As compared with patients without plaque, patients with plaque were older, had a longer duration of disease and more disease-related damage, and were less likely to have multiple autoantibodies or to have been treated with prednisone, cyclophosphamide, or hydroxychloroquine. In multivariate analyses including patients with lupus, independent predictors of plaque were a longer duration of disease, a higher damage-index score, a lower incidence of the use of cyclophosphamide, and the absence of anti-Smith antibodies.

CONCLUSIONS

Atherosclerosis occurs prematurely in patients with systemic lupus erythematosus and is independent of traditional risk factors for cardiovascular disease. The clinical profile of patients with lupus and atherosclerosis suggests a role for disease-related factors in atherogenesis and underscores the need for trials of more focused and effective anti-inflammatory therapy.

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THE DIAGNOSTIC CRITERIA FOR SYSTEMIC lupus erythematosus, the prototypical autoimmune disease, focus on its major clinical manifestations, particularly renal, neurologic, and hematologic disease. In 1976, Urowitz et al. noted premature myocardial infarction among patients with lupus,¹ a finding confirmed by subsequent studies.^{2,3}

However, the reported cardiovascular outcomes are based on relatively few events, and the prevalence of atherosclerosis among patients with lupus and its relation to that in a control population are unknown. Furthermore, controversy remains regarding the mechanism of premature atherosclerosis. The prevailing hypothesis holds that premature atherosclerosis in lupus is attributable to an increased frequency of conventional risk factors, such as hypertension, dyslipidemia, and diabetes, all of which may be provoked or exacerbated by corticosteroid therapy.⁴⁻⁶ A recent study,⁷ however, suggested that lupus itself may be atherogenic through chronic activation of the immune system. This hypothesis is supported by data demonstrating an inflammatory component in atherosclerosis in the general population.⁸⁻¹¹

In view of the profound alterations in immune function and inflammation that characterize lupus, we used a case-control approach to assess the prevalence of atherosclerosis and risk factors for cardiovascular disease in a population of patients with lupus. We hypothesized that atherosclerosis would be more prevalent among the patients and would not be attributable to traditional risk factors. We also assessed whether disease factors, treatment, and immune and inflammatory mediators are independently related to atherosclerosis in lupus.

METHODS

STUDY POPULATION

A total of 204 sequential nonhospitalized patients with systemic lupus erythematosus who were enrolled in the Autoimmune Disease Registry at the Hospital for Special Surgery in New York were recruited at the time of outpatient visits. Patients were recruited between April 1999 and October 2002. All patients met the diagnostic criteria of the American College of Rheumatology.¹² Patients were excluded if they were younger than 18 years of age, were pregnant, or had renal failure (defined by a serum creatinine level of 3.0 mg per deciliter [265 μ mol per

liter] or more or a creatinine clearance of no more than 30 ml per minute). Eight patients had preexisting clinical coronary disease: myocardial infarction in two (documented on the basis of segmental wall-motion abnormalities) and angina in six (as defined by abnormal results on coronary angiography in five and an abnormal perfusion study in one). Cerebrovascular disease was present in 17, of whom 8 had had a transient ischemic attack (including 1 with angina), and 9 had had a stroke.

Patients with lupus were individually matched to control subjects on the basis of age (within five years), sex, race, and hypertension status. Control subjects were drawn from normotensive and hypertensive subjects participating in studies performed at Cornell University and funded by the National Institutes of Health.^{13,14} These subjects were participants in studies that used a similar imaging protocol to examine the effect of job strain, aging, and hypertension on preclinical cardiovascular disease. The traditional risk factors assessed were the presence or absence of a family history of premature myocardial infarction (before 55 years of age in first-degree male relatives or before 65 years in female relatives), smoking status, the presence or absence of hypertension (as defined by a blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications), the presence or absence of diabetes mellitus, and the cholesterol level after an overnight fast. None of the control subjects had clinical evidence of myocardial infarction or cerebrovascular disease. Control subjects with hypertension were studied after antihypertensive medications had been withheld for at least three weeks. Brachial blood pressures were obtained immediately after the ultrasound studies. Of 204 patients with lupus, 6 young women could not be matched to suitable control subjects and 1 patient did not complete the study protocol owing to equipment failure.

All patients were interviewed and examined with the use of a standardized data-collection instrument. Disease activity and disease-related damage were assessed at the time of enrollment in the study with use of the Systemic Lupus Erythematosus Disease Activity Index¹⁵ and the Systemic Lupus International Collaborating Clinics damage index,¹⁶ respectively. Comprehensive medication histories were obtained through interviews with the patients and chart review. The use of corticosteroid therapy was categorized as current, former, or none and quantified in terms of the average daily dose over

the preceding five years. The study protocol was approved by the institutional review board; all participants gave written informed consent.

ULTRASONOGRAPHIC STUDIES

The extracranial carotid arteries were examined ultrasonographically with the use of a standardized protocol.¹⁴ In brief, both the right and left common, internal, and external carotid arteries were examined in multiple projections to identify the presence of atherosclerosis — that is, plaque, defined as a focal protrusion of more than 50 percent of the surrounding wall. The intimal–medial thickness and diameters of the common carotid arteries were measured from two-dimensionally guided M-mode images during several cycles, and the values were averaged. Carotid cross-sectional area, a measure of vascular volume or mass, was calculated as previously described.¹⁴

Echocardiography, performed with the use of standard techniques,¹⁷ included identification of the presence and degree of pulmonary hypertension from the peak velocity of the tricuspid regurgitation signal with use of the modified Bernoulli equation, the presence of Libman–Sacks lesions (focal leaflet thickening of a nature unlikely to represent age-related valvular thickening), and the presence of pericardial thickening, effusion, or both. All ultrasonographic studies were performed on the day of the study visit by an experienced research technician and interpreted by a single cardiologist who was unaware of the clinical characteristics of the patients and control subjects.

LABORATORY ASSESSMENT

Patients with lupus were assessed at the time of the study visit by means of routine chemical analyses; a complete blood count; measurement of Lp(a) lipoprotein by cholesterol content; measurement of serum complement (C3 and C4); tests for antibodies against double-stranded DNA, Smith (Sm), ribonuclear protein (RNP), and antiphospholipid antibody (considered positive if the level of either anticardiolipin IgG or IgM exceeded 40 isotype phospholipid units per milliliter or if lupus anticoagulant was present¹⁸); and a high sensitivity test for C-reactive protein. CD40 ligand in serum was measured as previously described.¹⁹ These tests were performed by the same clinical laboratory with use of assays that were invariant during the study period. Serum interleukin-6, tumor necrosis factor p55 receptor, and tumor necrosis factor p75 receptor were measured

with the use of kits (Biosource International). Soluble intracellular adhesion molecule 1 and vascular-cell adhesion molecule 1 were measured with an enzyme-linked immunosorbent assay. Fasting homocysteine levels were measured before and after the oral administration of 5 g of methionine.²⁰

STATISTICAL ANALYSIS

Comparisons between patients and control subjects and between patients with and those without atherosclerosis were made by means of two-sample t-tests or Mann–Whitney tests (in the case of non-normal distribution) for continuous variables and by chi-square analysis for categorical variables. The independence of the association with atherosclerosis was assessed with use of a stepwise, forward-selection logistic-regression procedure in which all variables that had a significant bivariate relation (as defined by a P value of less than 0.05) with the outcome were evaluated for inclusion in the model; results are reported as odds ratios with 95 percent confidence intervals. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

COMPARISON OF PATIENTS AND CONTROLS

The two groups were similar with respect to all demographic variables and risk factors for cardiovascular disease (Table 1) except blood pressure; the control subjects had higher blood pressure than the patients at the time of study. The overall prevalence of atherosclerosis (plaque) was higher among the patients than the controls (relative risk, 2.4; 95 percent confidence interval, 1.7 to 3.6; $P < 0.001$) in every age group (Fig. 1), especially the youngest age group; the prevalence was 5.6 times as high among patients less than 40 years of age as among control subjects in this age group. A similar trend was seen in older patients, but the small numbers in each group precluded the difference from being statistically significant. Intimal–medial thickness was significantly less and the luminal diameter was larger in the patients than in the controls (Table 1), resulting in a slight but significant reduction in vascular mass or carotid cross-sectional area.

In a multivariate analysis that included age, hypertension status, diabetes status, smoking status, fasting cholesterol level, and lupus status, only age (odds ratio, 2.4 per 10 years; 95 percent confidence interval, 1.8 to 3.1), the presence of lupus (odds ratio, 4.8; 95 percent confidence interval, 2.6 to 8.7),

Table 1. Characteristics of Patients with Systemic Lupus Erythematosus and Control Subjects.*

Characteristic	Patients (N=197)	Controls (N=197)	P Value
Age (yr)	44±13	44±12	—
Female sex (%)	94.4	94.4	—
White race (%)	55.8	57.9	—
Hypertension (%)	28.9	23.4	—
Body-mass index†	26.0±6.9	25.2±4.5	0.16
Blood pressure (mm Hg)			
Systolic	110±18	119±22	<0.001
Diastolic	71±10	74±13	0.002
Current smoker (%)	14.9	15.8	0.80
Diabetes (%)	3.7	1.5	0.18
Cholesterol (mg/dl)‡	208±50	206±44	0.69
Plaque (%)	37.1	15.2	<0.001
Features of common carotid arteries			
Intimal–medial thickness (mm)	0.61±0.16	0.67±0.14	<0.001
Diameter (mm)	5.4±0.62	5.2±0.55	<0.001
Cross-sectional area (mm ²)	11.7±3.8	12.4±3.6	0.05

* Plus–minus values are means ±SD.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

COMPARISON OF PATIENTS WITH AND THOSE WITHOUT ATHEROSCLEROTIC PLAQUE

In univariate analyses, patients with lupus who had plaque were older, were more likely to be white and postmenopausal, and had higher systolic blood pressures and total and low-density lipoprotein cholesterol levels than those without plaque (Table 2). Patients with plaque were older at the time of diagnosis, had had lupus longer, and had higher scores on the damage index. Twenty-two percent of the patients with plaque had damage-index scores of at least 4, as compared with 11 percent of the patients without plaque (P=0.03). Since the scores for the damage index may also represent adverse effects of therapy, we repeated the analyses using a revised index that excluded conditions such as cataracts, osteoporosis, ovarian failure, avascular necrosis, diabetes, alopecia, and cancer. The damage-index scores remained higher in patients with plaque than in those without plaque (1.2 vs. 0.8, P=0.07). Likewise, the scores remained higher in patients with plaque when coronary events were excluded (1.9 vs. 1.2, P=0.02). Patients with plaque were more likely to have pulmonary hypertension and preexisting coronary artery disease (angina or a history of myocardial infarction), but not clinical cerebrovascular disease, than patients without plaque.

Comparison of serologic markers of lupus showed that antibodies against Sm and RNP were less frequent in patients with plaque than in those without plaque; antibodies against any of the ribonuclear proteins (Sm, RNP, La, and Ro) were present in 60.2 percent of patients without plaque and in 40.8 percent of those with plaque (P=0.009). The frequency of anti–double-stranded DNA and any antiphospholipid antibodies did not differ significantly between patients with and those without plaque, nor were these antibodies associated with the presence of clinical coronary or cerebrovascular disease (data not shown). However, when the components of antiphospholipid-antibody status (anticardiolipin antibodies and lupus anticoagulant) were examined individually, anticardiolipin antibodies were less common in patients with plaque than in those without plaque.

Drug therapy differed between patients with plaque and those without plaque. Former or current treatment with prednisone tended to be less frequent in patients with plaque; the average dose of prednisone was also lower in these patients. Use of cyclophosphamide and hydroxychloroquine (defined as current or former) was lower in those with plaque.

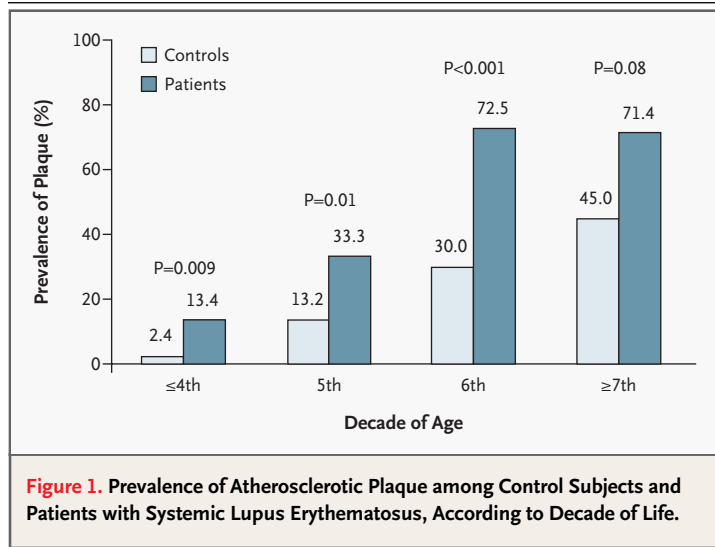


Figure 1. Prevalence of Atherosclerotic Plaque among Control Subjects and Patients with Systemic Lupus Erythematosus, According to Decade of Life.

and the serum cholesterol level (odds ratio, 1.1 per 10 mg per deciliter [0.26 mmol per liter]; 95 percent confidence interval, 1.0 to 1.5) were independently associated with atherosclerosis. The exclusion of patients with clinical cardiovascular disease and their controls did not alter the results.

There were no significant differences between the groups in the use of warfarin, nonsteroidal anti-inflammatory drugs, or lipid-lowering agents (data not shown).

The levels of inflammatory mediators associated with cardiovascular disease in the general population are compared in the two groups of patients in Table 3. Although average values were increased in the patients as a whole, there were no significant differences in the levels between patients with and those without plaque. Similarly, the presence of abnormal elevations of these mediators was not associated with plaque.

We used logistic-regression analyses to examine demographic variables and risk factors for cardiovascular disease that were significantly more common in patients with plaque than in those without plaque; only age remained in the model. A second analysis examined disease-related factors that were significant in univariate analyses; the age at diagnosis, the duration of disease, the damage-index score, and the presence of anti-Sm antibodies remained in the model. A final analysis (Table 4) added significant treatment variables to disease-related variables. Independent correlates of atherosclerosis included an older age at diagnosis, a longer duration of disease, a higher damage-index score, absence of the use of cyclophosphamide, and the absence of anti-Sm or anticardiolipin antibody. Restriction of analyses to patients who were younger than 35 years of age when the disease began confirmed the association of atherosclerosis with a longer duration of the disease, a higher damage-index score, and the lack of immunosuppressive therapy.

DISCUSSION

This case-control study assessed the presence or absence, magnitude, and determinants of atherosclerosis in patients with systemic lupus erythematosus in a population-based sample. The main findings, confirming those of our pilot study,²¹ are that the prevalence of atherosclerosis is significantly increased among patients with lupus and that this increase is not attributable to traditional risk factors for cardiovascular disease. Similar findings are reported elsewhere in this issue of the *Journal*.²² Our finding of an association of atherosclerosis with a longer duration of disease, a higher damage-index score, and less aggressive immunosuppressive therapy argues strongly that chronic inflammation is atherogenic in this population.

Table 2. Characteristics of Patients with Systemic Lupus Erythematosus, According to the Presence or Absence of Plaque.*

Characteristic	No Plaque (N=124)	Plaque (N=73)	P Value
Age (yr)	39±11	52±12	<0.001
White race (%)	47.6	67.1	0.008
Postmenopausal (%)	35.0	72.0	<0.001
Body-mass index	25.8±7.0	26.4±6.6	0.53
Systolic blood pressure (mm Hg)	107±15	116±21	<0.001
Current smoker (%)	16.2	12.7	0.51
Hypertension (%)	24.2	37.0	0.06
Diabetes (%)	1.7	7.1	0.06
Family history of premature MI (%)	13.9	21.1	0.33
Cholesterol (mg/dl) †			
Total	201±51	219±46	0.005
Low-density lipoprotein	113±46	125±40	0.01
Lp(a) lipoprotein (mg/dl)	36±34	36±36	0.63
Homocysteine (mg/dl)			
Before methionine loading	7.3±2.9	8.6±4.3	0.06
After methionine loading	9.5±15.1	12.4±27.8	0.23
Age at diagnosis (yr)	28±11	38±13	<0.001
Duration of disease (mo)	129±99	173±116	0.01
Disease-activity-index score ‡	4.6±5.3	3.2±4.7	0.07
Damage-index score §	1.2±1.8	2.0±2.5	0.006
Raynaud's phenomenon (%)	45.6	58.0	0.11
Valvular lesions (%)	5.9	11.3	0.19
Pulmonary hypertension (%)	11.3	27.4	0.004
Coronary artery disease (%)	0	11.4	<0.001
Cerebrovascular disease (%)	8.6	15.7	0.40
Renal involvement (%) ¶	38.7	27.4	0.11
Antiphospholipid antibodies (%)	18.0	14.1	0.48
Lupus anticoagulant	10.4	15.3	0.37
Anticardiolipin antibody	11.5	2.8	0.04
Anti-RNP (%)	31.7	14.1	0.007
Anti-Sm (%)	14.6	1.4	0.003
Anti-double-stranded DNA (%)	36.6	50.4	0.33
C3 (mg/dl)	92±32	97±32	0.33
C4 (mg/dl)	18±8	21±9	0.13
Prednisone use (%)	92.6	84.9	0.09
5-yr daily dose of prednisone (mg)	11.9±6.9	6.9±6.8	0.002
Duration of corticosteroid use (mo)	67±75	91±94	0.24
Azathioprine use (%)	36.4	24.2	0.10
Cyclophosphamide use (%)	26.0	9.6	0.005
Hydroxychloroquine use (%)	82.3	63.0	0.003

* Plus-minus values are means ±SD. MI denotes myocardial infarction.

† To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

‡ Scores can range from 0 to 105, with higher scores indicating greater disease activity.

§ Scores can range from 0 to 46, with higher scores indicating greater disease-related damage.

¶ Renal involvement was defined on the basis of American College of Rheumatology diagnostic criteria.

|| "Use" indicates current or former use of medication.

Table 3. Comparison of Serum Levels of Inflammatory Mediators in Patients with Systemic Lupus Erythematosus, According to the Presence or Absence of Plaque.*

Variable	Upper Limit of Normal†	% Above Upper Limit of Normal	Patients without Plaque (N=124)	Patients with Plaque (N=73)	P Value
C-reactive protein (mg/dl)	3.0	41.5	4.9±7.4	5.9±9.0	0.31
Interleukin-6 (pg/ml)	5.0	54.1	8.8±15.9	6.2±7.1	0.34
Tumor necrosis factor (ng/ml)					
p55 receptor	1.7	35.5	1.6±0.85	1.9±1.6	0.66
p75 receptor	5.5	25.7	5.5±11.8	4.3±2.6	0.58
CD40 ligand (ng/ml)	15.0‡	17.9	11.0±8.3	9.9±7.5	0.44
Intracellular adhesion molecule 1 (ng/ml)	103	65.4	124±47	151±214	0.72
Vascular-cell adhesion molecule 1 (ng/ml)	714‡	22.3	693±273	720±267	0.41

* Plus-minus values are means ±SD.

† Unless otherwise stated, the upper limit of normal is defined as the upper limit of the normal range according to the assay manufacturer or high-risk threshold in the case of C-reactive protein.

‡ The upper limit of normal is defined as 2 SD above the mean.

We determined the correlates of preclinical atherosclerosis in patients with systemic lupus erythematosus. One previous case-control study²³ found greater carotid intimal-medial thickness in patients with lupus who had had a myocardial infarction, angina, stroke, or claudication than in those without clinical cardiovascular disease. The small sample size (26 in each group) precluded a determination of the prevalence and independent correlates of atherosclerosis. An observational study of women enrolled in the Pittsburgh Lupus Registry reported a prevalence of plaque that was similar to that in our study (40 percent and 37 percent, respectively);

the risk of plaque was independently related to older age, higher systolic blood pressure, a higher level of low-density cholesterol, and a history of myocardial infarction or angina.²⁴ Differences between these findings and ours may relate to the higher proportion of whites in the Pittsburgh study (87 percent and 55 percent, respectively) and the greater prevalence of clinical coronary disease (8.6 percent and 3.9 percent, respectively).

Interestingly, although the Pittsburgh study²⁴ did not include a control population, the mean intimal-medial thickness in women with lupus was slightly lower than that in women participating in the Women's Healthy Lifestyle Project conducted at the same institution (0.68 mm vs. 0.71 mm). This observation is similar to our finding in a case-control study and demonstrates the potential for dissociation between intimal-medial thickness, commonly considered a marker of early or diffuse atherosclerosis, and unequivocal evidence of atherosclerosis (i.e., plaque). The presence of plaque is a more potent predictor of clinical events, usually myocardial infarction, than is intimal-medial thickness.^{25,26} The independent association of atherosclerosis with the duration of disease and extent of disease-induced damage is noteworthy, because the damage index is a marker of the cumulative severity of disease.

In the general population, increased serum levels of C-reactive protein, intracellular adhesion molecule 1, and CD40 ligand are associated with an increased risk of cardiovascular events.⁸⁻¹¹ Although

Table 4. Logistic-Regression Analysis of Independent Predictors of Atherosclerosis in Patients with Systemic Lupus Erythematosus.

Variable	Beta Coefficient	Odds Ratio (95% CI)*	P Value
Age at diagnosis (per 10 yr)	0.93	2.52 (1.74-3.65)	<0.001
Disease duration (per 10 yr)	0.76	2.14 (1.28-3.57)	0.004
Damage-index score (per point)†	0.23	1.26 (1.03-1.55)	0.03
Cyclophosphamide use	-1.17	0.31 (0.10-0.96)	0.04
Anti-Sm antibody‡	-2.21	0.11 (0.01-0.98)	0.05
Hydroxychloroquine use	-0.71	0.49 (0.21-1.12)	0.09

* CI denotes confidence interval.

† Scores can range from 0 to 46, with higher scores indicating greater disease-related damage.

‡ Similar results were obtained when anticardiolipin antibody was substituted for anti-Smith antibody (i.e., there was a negative association between the presence of autoantibody and plaque; P=0.01).

these inflammatory mediators were elevated in our patients with lupus who had plaque, there were no significant differences between these patients and those without plaque. This finding suggests that these markers lose their discriminatory power with respect to cardiovascular outcomes among patients with conditions in which levels of inflammatory molecules are elevated, such as lupus, in contrast to the general population, where most values fall within the normal range. Nevertheless, levels of these markers of inflammation were abnormal in many patients with lupus, and longitudinal, rather than cross-sectional, studies may yet define their relation to the development and progression of atherosclerosis.

Although inflammatory mediators were not related to atherosclerosis in our patients, our data show that anti-Sm, anti-RNP, and anticardiolipin antibodies were less frequent in patients with plaque than in those without plaque. Although antiphospholipid antibodies have been implicated in atherogenesis,²⁷ possibly as a result of their activation of endothelial cells,²⁸ our study, as well as those of others, found no association between anticardiolipin antibody and carotid plaque^{24,29} or cardiovascular disease.²³ The clinical features and autoantibody specificities that differentiate patients with lupus who have plaque from those who do not have plaque may define two patterns of lupus: one characterized by more prolonged and seemingly less virulent disease that fosters atherosclerosis and the other by more prominent autoimmunity and aggressive disease, which is more likely to be treated with immunosuppressive therapies.

That treatment with corticosteroids may have a role in modifying the pathogenesis of atherosclerosis in systemic lupus erythematosus has been suggested.^{4,5} However, the average five-year daily dose of prednisone was actually significantly lower in our patients with lupus who had plaque. The significant negative relation between the use of hydroxychloroquine and the presence of atherosclerosis, even with high rates of use, is also striking. This trend has been noted before⁴ and has been attributed to reduced serum cholesterol levels.³⁰ In our study, cholesterol levels were similar in patients who had taken hydroxychloroquine and those who had not.

The limitations of our study include difficulties in accurately quantifying the severity of disease and disease treatment. Systemic lupus erythematosus is a chronic disease characterized by exacerbations

and remissions; thus, measures of disease activity, laboratory assays, and therapy vary with time. However, scores for the disease-activity index, measured at the time of study, did not differ significantly between patients with plaque and those without plaque, whereas the damage-index score, a summation of the cumulative effects of disease, was greater in patients with plaque, associating chronic tissue damage with atherogenesis. Although we cannot exclude the possibility that our population had more severe disease than the overall population of patients with lupus, the prevalence of clinical cardiovascular disease in our study was similar to the rates reported by other North American registries.^{4,7,24} Our case-control design precluded the identification of a causal relation between disease factors and atherosclerosis.

In conclusion, systemic lupus erythematosus is associated with an increased prevalence of atherosclerosis, which was most striking in young patients. Although the traditional risk factors for cardiovascular disease are not primarily responsible for such an accelerated development of atherosclerosis, their importance in the population as a whole is well established, and their role in the progression of atherosclerosis could not be examined in this cross-sectional study. Thus, it is prudent to identify and treat traditional risk factors aggressively in all patients with lupus.³¹

In our study, the presence of systemic lupus erythematosus was the most important independent correlate of atherosclerosis other than age. Our results suggest two clinical patterns of lupus, one characterized by smoldering disease with higher damage-index scores, limited production of autoantibodies, and atherosclerosis, and the other with a wider autoantibody spectrum, associated with more aggressive immunosuppressive therapy and a lower likelihood of plaque.

The negative correlation between atherosclerosis and aggressive therapy suggests that more vigorous therapy might decrease the likelihood and burden of atherosclerosis in patients with lupus and, perhaps, in those with other chronic inflammatory diseases. Our results also suggest that the use of immunosuppressive therapy primarily for clinical flares may not adequately control the chronic atherogenic inflammatory milieu. The identification of biologic markers of disease activity associated with atherosclerosis may help optimize therapy for this important manifestation of systemic autoimmune disease.

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REFERENCES

- Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 1976;60:221-5.
- Johnsson H, Nived O, Sturfelt G. Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine (Baltimore)* 1989;68:141-50.
- Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145:408-15.
- Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992;93:513-9.
- Petri M, Sepnce D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine (Baltimore)* 1992;71:291-302.
- Petri M, Roubenoff R, Dallal G, Nadeau MR, Selhub J, Rosenberg IH. Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. *Lancet* 1996;348:1120-4.
- Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331-7.
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973-9. [Erratum, *N Engl J Med* 1997;337:356.]
- Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98:731-3.
- Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet* 1998;351:88-92.
- Schönbeck U, Varo N, Libby P, Buring J, Ridker PM. Soluble CD40L and cardiovascular risk in women. *Circulation* 2001;104:2266-8.
- Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
- Schnall PL, Schwartz JE, Landsbergis PA, Warren K, Pickering TG. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. *Psychosom Med* 1998;60:697-706.
- Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB. Relation of arterial structure and function to left ventricular geometric patterns in hypertensive adults. *J Am Coll Cardiol* 1996;28:751-6. [Erratum, *J Am Coll Cardiol* 1996;28:1642.]
- Petri M, Buyon J, Skovron ML, Kim M. Reliability of SLEDAI and flare as clinical trial outcome measures. *Arthritis Rheum* 1998;41:Suppl:S218. abstract.
- Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363-9.
- Devereux RB, Roman MJ. Evaluation of cardiac and vascular structure and function by echocardiography and other noninvasive techniques. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis, and management. Vol. 2. New York: Raven Press, 1995:1969-85.
- Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999;42:1309-11.
- Vakkalanka RK, Woo C, Kirou KA, Koshy M, Berger D, Crow MK. Elevated levels and functional capacity of soluble CD40 ligand in systemic lupus erythematosus sera. *Arthritis Rheum* 1999;42:871-81.
- Ueland PM, Refsum H, Stabler SP, Malinow MR, Andersson A, Allen RH. Total homocysteine in plasma or serum: methods and clinical applications. *Clin Chem* 1993;39:1764-79.
- Roman MJ, Salmon JE, Sobel R, et al. Prevalence and relation to risk factors of carotid atherosclerosis and left ventricular hypertrophy in systemic lupus erythematosus and antiphospholipid antibody syndrome. *Am J Cardiol* 2001;87:663-6.
- Asanuma Y, Oeser A, Shintani AK, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2407-15.
- Svenungsson E, Jensen-Ustad K, Heimburger M, et al. Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation* 2001;104:1887-93.
- Manzi S, Selzer F, Sutton-Tyrrell, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:51-60.
- Belcaro G, Nicolaides AN, Laurora G, et al. Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. *Arterioscler Thromb Vasc Biol* 1996;16:851-6.
- Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* 1993;87:Suppl:II-56-II-65.
- Vaarala O. Autoantibodies to modified LDLs and other phospholipid-protein complexes as markers of cardiovascular diseases. *J Intern Med* 2000;247:381-4.
- Simantov R, LaSala JM, Lo SK, et al. Activation of cultured vascular endothelial cells by antiphospholipid antibodies. *J Clin Invest* 1995;96:2211-9.
- Petri M, Maksimowicz K, Magder L. Predictors of carotid atherosclerosis (plaque) in SLE: an inception cohort. *Arthritis Rheum* 2002;46:Suppl:S458-S459. abstract.
- Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. *Am J Med* 1994;96:254-9.
- Salmon JE, Roman MJ. Accelerated atherosclerosis in systemic lupus erythematosus: implications for patient management. *Curr Opin Rheumatol* 2001;13:341-4.

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CORRECTION

**Prevalence and Correlates of Accelerated
Atherosclerosis in Systemic Lupus Erythematosus**

Prevalence and Correlates of Accelerated Atherosclerosis in Systemic Lupus Erythematosus . On page 2403, in Table 2, the 12th entry should have read "Homocysteine ($\mu\text{mol/liter}$)," not "Homocysteine (mg/dl)," as printed.