

Comparison of Risk Factors for Vascular Disease in the Carotid Artery and Aorta in Women With Systemic Lupus Erythematosus

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Objective. To examine and compare risk factors for various stages of subclinical vascular disease in different vascular beds (carotid and aorta) in women with systemic lupus erythematosus (SLE) who have not yet developed clinical cardiovascular disease.

Methods. This cross-sectional study was conducted in 214 women without clinical cardiovascular disease who were enrolled in the Pittsburgh Lupus Registry. B-mode ultrasound was used to measure carotid plaque and intima-media wall thickness (IMT). Doppler probes were used to collect pulse-wave velocity waveforms from the right carotid and femoral arteries as a measure of aortic stiffness. All risk factor data were collected on the day of the ultrasound examinations.

Results. The mean \pm SD age of the women was 45.2 ± 10.5 years and the median SLE disease duration was ~ 9 years. Sixty-eight (32%) of the women had at least 1 focal plaque. The mean \pm SD IMT was 0.71 ± 0.1 mm, and the mean \pm SD pulse-wave velocity was 5.96 ± 1.6 meters/second. Using logistic regression, we found that determinants of plaque included older age, higher systolic blood pressure, lower levels of high-density lipoprotein 3, and antidepressant use. Determinants of plaque severity were older age, higher systolic blood

pressure, lower levels of albumin, and smoking. Independent determinants of the highest quartile of IMT were older age, higher pulse pressure, lower levels of albumin, elevated C-reactive protein levels, high cholesterol, and higher levels of glucose. Higher aortic stiffness was associated with older age, higher systolic blood pressure, higher C3 levels, lower white blood cell count, higher insulin levels, and renal disease.

Conclusion. In women with SLE, the risk factors associated with carotid plaque and IMT are those typically associated with cardiovascular disease in the general population, whereas the risk factors associated with vascular stiffness include SLE-specific variables related to immune dysregulation and complement metabolism. The high prevalence of cardiovascular disease among lupus patients may result from both early adverse effects on vascular stiffening as well as later promotion of wall thickening and plaque through inflammatory-mediated processes. These observations provide clues for future mechanistic studies.

Systemic lupus erythematosus (SLE) affects primarily women and causes chronic vascular inflammation. Women with SLE, particularly those under age 45 years, experience higher than expected rates of clinical cardiovascular disease, i.e., hypertension (1–3), myocardial infarction (1,4), and stroke (4). In addition to traditional cardiovascular risk factors, other factors specifically associated with SLE appear to be equally, if not more, important (5,6). It is likely that these factors are related to the underlying immune-mediated, inflammatory processes inherent in SLE.

Although the pathogenesis of vascular disease in SLE is unknown, it is thought to be multifactorial and of atherosclerotic origin. Atherosclerosis involves both atherosclerosis (fatty degeneration) and sclerosis (vessel stiffening). Both of these processes can be evaluated with

Supported by the Arthritis Foundation, a grant-in-aid from the American Heart Association, the Pennsylvania Chapter of the Lupus Foundation of America, and grants from the NIH (grant 1-P60-AR-44811-01 from the Multipurpose Arthritis Center, grant 5-M01-RR-00056 from the National Center for Research Resources/General Clinical Research Center, and grants 5R-01-HL-5490002, R01-AR-46588-01, and K24-AR-02213).

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Submitted for publication February 12, 2003; accepted in revised form September 4, 2003.

noninvasive ultrasound imaging techniques. Atherosclerosis in the carotid arteries is evaluated using B-mode ultrasound, which measures the degree of focal plaque and intima-media wall thickness (IMT) (7). Vascular stiffness is evaluated using pulse-wave velocity (PWV), which measures the rate at which arterial pulse waves move along the vessel (8). Plaque and IMT are measures of the structural properties of the arterial wall, whereas vascular stiffness is a measure of the functional properties. Longitudinal studies have shown that all 3 of these subclinical measures of cardiovascular disease are significant predictors of future cardiovascular events and mortality (9–12).

In a previous study, we used B-mode ultrasound to evaluate carotid plaque and IMT among 175 unselected women with SLE (13). We found that 40% of those women had evidence of focal carotid plaque and that their IMT was 0.71 ± 0.14 mm (mean \pm SD). Because that study included women who had experienced a prior clinical coronary event, it did not evaluate subclinical cardiovascular disease exclusively and represented a different end of the spectrum of severity.

When we used PWV to evaluate aortic stiffness in women with SLE, we found that traditional cardiovascular risk factors predominated among the postmenopausal women, but a mix of traditional and SLE-specific factors predominated among the younger, premenopausal women (5). The SLE-related factors included leukopenia, serum C3 levels, double-stranded DNA (dsDNA) antibodies, and nonuse of hydroxychloroquine. These results suggest that the associations between SLE-related factors and aortic stiffness might contribute to the premature cardiovascular disease observed among younger women with SLE. Early in the disease process, SLE may cause stiffening of the vascular wall that then sets the stage, as these women age, for an acceleration of the atherogenic process by the traditional risk factors.

Epidemiologic studies to identify the risk factors associated with subclinical vascular disease in different vascular beds and in different stages of the process will provide important foundational information for investigating the mechanisms by which these factors may function in the development of overt cardiovascular events. In particular, identifying factors specific to SLE may help to focus mechanistic studies on the premature development of cardiovascular disease in these young women.

The present study was designed to extend and improve on our previous studies by examining and comparing risk factors for various stages of subclinical

vascular disease in different vascular beds (carotid and aorta) in 214 women with SLE who were free from clinical cardiovascular disease and who have been well characterized with respect to both SLE and cardiovascular risk factors.

PATIENTS AND METHODS

Study population. The women recruited for this study are currently enrolled in the Pittsburgh Lupus Registry. At the time of enrollment, the registry included 983 living participants. The registry includes patients examined by University of Pittsburgh Medical Center rheumatologists and by rheumatologists working in the Pittsburgh metropolitan area. All women in the registry must fulfill the 1982 American College of Rheumatology revised criteria for the classification of definite or probable SLE (14). The updated criteria for SLE (15) had not yet been published when the study began. All eligible women who were 18 years of age or older were invited to participate, regardless of their history of cardiovascular events. The first 300 women to respond were enrolled in our original cardiovascular study. The analyses described in the present report include only the women who had not experienced a confirmed myocardial infarction or stroke or did not have a physician diagnosis of angina or transient ischemic attack. Each participant provided an authorization for release of medical information so that pertinent hospital and outpatient records could be reviewed to confirm the aforementioned events. Criteria for defining a myocardial infarction, stroke, angina, and transient ischemic attack were taken from the Cardiovascular Health Study (16). The University of Pittsburgh's Institutional Review Board approved this study, and all women provided written informed consent.

Variable measurements. Participation in this study consisted of an interview, a physical examination, and laboratory and ultrasound tests. All risk factor data were collected on the same day as the ultrasound examinations.

Traditional cardiovascular risk factors. The clinic visit included anthropomorphic measurements (height, weight, and waist and hip circumference), 2 consecutive blood pressure readings (with patients seated), and a blood draw after a required fasting period. Blood samples were used to measure total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (HDL and HDL-3 subfractions), and triglycerides, at the Lipid Laboratory in the University of Pittsburgh Graduate School of Public Health, which has been certified by the Centers for Disease Control and Prevention. The Friedewald equation was used to estimate LDL cholesterol (17). Plasma glucose levels were determined by enzymatic assay, and plasma insulin levels were measured by radioimmunoassay. Hypertension was defined as an average systolic blood pressure ≥ 140 mm Hg or an average diastolic blood pressure ≥ 90 mm Hg or the use of antihypertensive agents. Information was also collected on age, race, education, smoking habits, family history of cardiovascular disease (myocardial infarction or stroke in a first-degree relative before the age of 60 years), menopausal status (when menopausal status was uncertain, follicle-stimulating hormone levels were obtained), estrogen replacement, and diabetes.

SLE-related disease factors. SLE disease activity and cumulative organ damage were measured by the same physician using the Systemic Lupus Disease Activity Measure (18) and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC) damage index (19). In addition, the women provided information on corticosteroid treatment (current use, maximum dose, and duration of use) and current use of hydroxychloroquine, immunosuppressants, and antidepressants. Renal disease was defined using the SLICC renal variables, which requires the presence of nephrotic-range proteinuria (≥ 3.5 grams/24 hours) or renal insufficiency (glomerular filtration rate $< 50\%$) for at least 6 months. Laboratory studies included tests for lupus anticoagulant (partial thromboplastin time or Russell's viper venom time with mix), C3, C4, anticardiolipin antibodies (IgG > 15 standard IgG phospholipid units, IgM > 10 standard IgM phospholipid units; Incstar, Stillwater, MN), and native DNA (dsDNA) antibodies (by *Crithidia luciliae*).

Inflammatory markers. Fibrinogen was measured using a modified clot-rate assay, while an enzyme-linked immunosorbent assay was used for determination of C-reactive protein (CRP) and a dye binding assay for albumin (20).

Carotid atherosclerosis and intima-media wall thickness. Carotid ultrasound was performed as previously described (13). Briefly, a Toshiba SSA-270A scanner (Tustin, CA) equipped with a 5-mHz linear array imaging probe was used to image the carotid arteries. Sonographers scanned the right and left common carotid artery, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. Plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the surrounding areas. For each segment, the degree of plaque was graded between 0 (no observable plaque) and 3 (plaque covering 50% or more of the vessel diameter). The grades from all 10 segments of the combined left and right carotid artery were summed to create the plaque index (possible range 0–30). The plaque index was found to be a valid and reproducible measure of carotid atherosclerosis in a number of populations (21).

Readers also measured the average IMT across 1-cm segments of both the right and left sides of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and internal carotid artery. Values from each location were then averaged to produce an overall measure of IMT. We have previously documented the reproducibility of carotid duplex scanning in general and also among our study population at the University of Pittsburgh Ultrasound Laboratory (13,22).

Aortic stiffness. For the determination of aortic stiffness, simultaneous recordings of the arterial flow waves from the right common carotid artery and the right femoral artery were made by using nondirectional transcutaneous Doppler flow probes (10 mHz, model 810-a; Parks Medical Electronics, Aloha, OR) (5). PWV measurements were derived from visual flow waves generated by ultrasound reflections off the moving column of blood. Three consecutive sets of waveforms were collected per participant. Aortic PWV was determined from the foot to foot flow-wave velocity (23). At least 10 flow waves were averaged into 1 final waveform using the peak of the R-wave from the simultaneously recorded electrocardiogram as a timing marker. Distance measurements between the carotid and femoral sampling sites were taken using a standard

tape measure. The following 3 measurements were made: 1) from the midpoint of the manubrium sterni to the lower edge of the umbilicus; 2) from the edge of the umbilicus to the femoral artery sampling site; and 3) from the midpoint of the manubrium sterni to the sampling site on the carotid. The third distance was subtracted from the sum of the first 2 distances. The PWV was calculated by dividing the distance component by the time component. We have previously documented the reproducibility of this method in general, as well as among our study population (5,24).

Statistical analysis. The descriptive analyses were stratified by focal carotid plaque status (absence versus presence) and summarized as means or medians (for nonnormally distributed variables) for continuous variables and as percentages for categorical variables. Intergroup differences of continuous variables were analyzed by *t*-tests for normally distributed variables and Wilcoxon's rank sum test for nonparametric factors. Chi-square tests or Fisher's exact test were used to evaluate categorical variables. Continuous risk factors were either in their original forms or were split into categories based on means, quartiles, or natural cut-off points, which were determined using moving averages, a smoothing technique and graphic aid. The outcomes for this study included the presence (yes/no) and severity (plaque index 0, 1, 2, or ≥ 3) of carotid atherosclerosis, IMT (top quartile versus lower quartiles), and PWV (top quartile versus lower quartiles). The association between all 3 outcomes was evaluated by Spearman's correlations.

The Cochran–Mantel–Haenszel test for trend was used to evaluate the linear association between age groups and each outcome (25). Stepwise logistic regression was used to build models evaluating risk factors related to the presence of focal plaque as well as to the top quartile of both IMT and PWV. Logistic regression was also used to identify risk factors in women at highest risk (women with carotid plaque who also ranked in the highest quartile for both IMT and PWV) versus all other women. Polychotomous logistic regression was used to evaluate risk factors associated with severity of focal plaque. For all models, baseline demographic and clinical variables were initially screened univariately, the outcomes of interest being those with a *P* value less than 0.15. These variables were then assessed in a forward stepwise manner. All 2-way interactions were evaluated. Model assumptions (Hosmer and Lemeshow goodness-of-fit [26] and score test for proportional odds) were met based on standard assessments.

RESULTS

Patient population. A total of 300 women were enrolled in the original cardiovascular study. Of these, 270 women were free from cardiovascular events and eligible for the current analyses. Of the 270 eligible women, 214 women had usable data from all 3 ultrasound examinations. The remaining 56 women either had unclear waveforms or did not undergo the procedure because of refusal, equipment failure, or time constraints. The 214 partici-

Table 1. Demographic, disease, and cardiovascular characteristics in 214 women with systemic lupus erythematosus (SLE) stratified by plaque status*

Variable	Plaque (n = 68)	No plaque (n = 146)	Overall (n = 214)
Age, years	52.6 ± 9.7†	41.8 ± 9.0	45.2 ± 10.5
Race, % white	89.7	91.1	90.7
Smokers, %	16.2	11.6	13.1
Education, years	13.6 ± 2.0‡	14.3 ± 2.1	14.0 ± 2.1
Postmenopausal, %	69.1†	31.5	43.5
Body mass index, kg/m ²	29.2 ± 7.1‡	26.9 ± 6.2	27.6 ± 6.6
Waist circumference, cm	92.2 ± 15.5	88.3 ± 18.1	89.6 ± 17.4
Median SLE duration, years	10.9§	8.2	9.1
SLE cumulative organ damage	1.6 ± 1.8§	1.2 ± 1.6	1.3 ± 1.6
SLE activity score	6.0 ± 2.9†	7.3 ± 4.0	6.9 ± 3.7
Median steroid duration, years	4.0†	2.0	3.0
% currently taking medication			
Prednisone	42.7	41.1	41.6
Hydroxychloroquine	48.5	45.2	46.3
Immunosuppressives¶	13.2	14.4	14.0
Antidepressants	27.9‡	14.4	18.7
Anti-dsDNA, %	19.4	19.3	19.3
Anticardiolipin antibodies, %	19.4	17.2	17.9
Lupus anticoagulant, %	29.9	21.4	24.1
C3, mg/dl	95.4 ± 24.8	94.7 ± 23.9	94.9 ± 24.1
C4, mg/dl	21.9 ± 8.0	21.1 ± 7.0	21.4 ± 7.3
Intima-media wall thickness, mm	0.81 ± 0.2†	0.66 ± 0.1	0.71 ± 0.1
Pulse-wave velocity, meters/second	6.96 ± 2.0†	5.49 ± 1.1	5.96 ± 1.6
Systolic BP, mm Hg	131.1 ± 19.5†	116.0 ± 15.7	120.8 ± 18.4
Diastolic BP, mm Hg	81.6 ± 9.8†	76.6 ± 10.6	78.2 ± 10.6
Hypertension, % [#]	50.0†	29.5	36.0
Pulse pressure, mm Hg	49.5 ± 16.1†	39.4 ± 9.9	42.6 ± 13.1
Cholesterol, mg/dl	203.0 ± 37.7‡	190.0 ± 43.8	194.1 ± 42.4
LDL cholesterol, mg/dl	117.8 ± 33.3§	108.3 ± 34.4	111.3 ± 34.3
HDL cholesterol, mg/dl	57.9 ± 17.2	56.7 ± 16.2	57.1 ± 16.5
Median triglycerides, mg/dl	128.0†	99.0	108.0
Glucose, mg/dl	101.4 ± 17.9	99.6 ± 30.2	100.2 ± 27.0
Insulin, μU/ml	18.6 ± 9.5	17.4 ± 9.9	17.8 ± 9.8
White cell count, 10 ³ /mm ³	5.71 ± 2.2	5.59 ± 2.0	5.67 ± 2.2
Median CRP, mg/ml	2.6†	1.6	2.0
Median fibrinogen, mg/dl	304.0§	285.0	293.5
Albumin, gm/dl	4.6 ± 0.4	4.7 ± 0.4	4.7 ± 0.4
Renal disease, %	10.3	10.3	10.3

* Except where otherwise indicated, values are the mean ± SD. Intergroup differences of continuous variables were analyzed by *t*-tests for normally distributed variables and Wilcoxon's rank sum test for nonparametric factors. dsDNA = double-stranded DNA; BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein.

† *P* ≤ 0.01 versus those with no plaque.

‡ *P* ≤ 0.05 versus those with no plaque.

§ *P* ≤ 0.10 versus those with no plaque.

¶ Immunosuppressive agents included cyclophosphamide, azathioprine, methotrexate, cyclosporine, or FK506.

Women were considered to have hypertension if they were taking antihypertensive medication or their sitting systolic blood pressure was >140 mm Hg or their diastolic blood pressure was >90 mm Hg.

pants were slightly older than the 56 women with missing PWV data (mean ± SD age 45.2 ± 10.5 years versus 43.8 ± 11.7 years), although the difference was not significant. Likewise, there were no differences between those women included and those excluded in terms of SLE activity, SLE cumulative organ damage, SLE duration, menopausal status, mean blood pressure, and presence of

carotid plaque. Compared with all women in the Pittsburgh Lupus Registry (n = 983), the 214 study participants were younger (mean ± SD 45.2 ± 10.5 years versus 51.8 ± 14.7 years; *P* < 0.01), had a shorter duration of SLE (mean ± SD 10.5 ± 7.0 years versus 14.8 ± 7.1 years; *P* < 0.01), and were less likely to be African American (90.7% versus 84.4% white; *P* < 0.05).

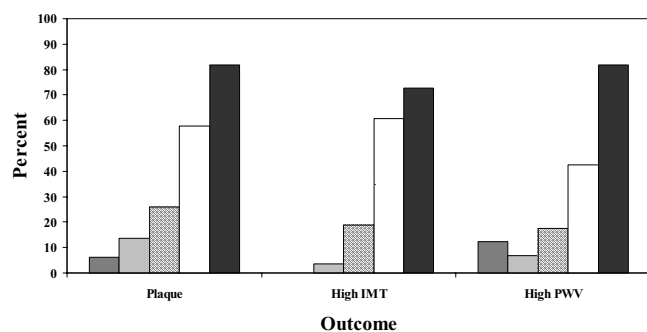


Figure 1. The prevalence of carotid plaque, the highest quartile of intima-media wall thickness (IMT), and the highest quartile of pulse-wave velocity (PWV) among women with systemic lupus erythematosus, by age category (≤ 30 years [dark gray bar], 31–40 years [light gray bar], 41–50 years [cross-hatched bar], 51–60 years [open bar], ≥ 60 years [solid bar]). Each of the outcomes was significantly associated with increasing age ($P = 0.001$, test for trend).

Demographic and SLE characteristics. Of the 214 women, who were predominantly nonsmokers (Table 1), there were 68 participants (32%) with evidence of focal plaque. These women with carotid plaque were significantly older, less educated, more likely to be postmenopausal, and heavier than were the women without plaque. The median SLE disease duration was longer in the women with carotid plaque. These women also had a higher cumulative organ damage score and lower SLE activity score, took prednisone for a longer number of years, and were more likely to be taking antidepressants. Approximately 20% of the 214 women were positive for antibodies to native DNA (anti-dsDNA) and to cardiolipin, and $\sim 25\%$ were positive for lupus anticoagulant.

Cardiovascular and inflammatory marker characteristics. The 68 women with plaque (32%) had significantly thicker carotid arteries (IMT) and stiffer

aortas (PWV) than did the women without carotid plaque (Table 1). The women with plaque also had a significantly higher mean blood pressure and pulse pressure and were more likely to have hypertension than were those free from plaque. Likewise, a higher proportion of women with plaque were taking antihypertensive medications (40% versus 23% of those without plaque; $P < 0.01$). The women with plaque had significantly higher mean total cholesterol levels and higher median triglyceride levels than did the women without plaque. They also had higher median levels of the inflammatory markers CRP and fibrinogen.

The association between each outcome and age is depicted in Figure 1. In general, there was an increase in the prevalence of plaque with increasing age, as well as an increase in the percentage of women in the top quartile of IMT and top quartile of PWV with older age ($P = 0.001$, test for trend for each outcome). In addition, we evaluated the pairwise relationship between all 3 outcomes. Although all 3 were highly correlated, the strongest association was between plaque and IMT ($r = 0.56$), the weakest association was between IMT and PWV ($r = 0.36$), and the correlation between plaque and PWV was 0.41; all correlations were statistically significant ($P < 0.0001$). The relative strengths of these associations were further evidenced by the observation that the largest number of women ($n = 16$) had both plaque and high IMT, fewer women ($n = 10$) had plaque and high PWV, and the least number of women ($n = 4$) had high IMT and high PWV.

Carotid plaque. Thirty-two percent of the women in this study had evidence of focal carotid plaque. Of these, 50% had a plaque index of 1, 19% had a plaque index of 2, and 31% had a plaque index ≥ 3 (plaque index range 1–16). These plaque severity categories were created on the basis of our sample size. The best model of risk factors associated with the presence of

Table 2. Logistic regression analysis of variables associated with the presence and severity of focal carotid plaque in women with systemic lupus erythematosus*

Explanatory variable	Presence of carotid plaque			Severity of carotid plaque		
	Odds ratio	95% CI	<i>P</i>	Odds ratio	95% CI	<i>P</i>
Age, years	1.12	1.07–1.17	<0.001	1.11	1.07–1.18	<0.001
Systolic blood pressure, mm Hg	1.03	1.01–1.06	0.007	1.03	1.01–1.06	0.002
Antidepressant use, yes/no	2.15	0.93–4.97	0.07	–	–	–
HDL-3, mg/dl	0.96	0.93–0.99	0.04	–	–	–
Albumin ≤ 3.9 gm/dl	–	–	–	5.23	1.35–20.17	0.02
Ever smoked	–	–	–	1.90	1.00–3.62	0.05

* Focal carotid plaque was defined as follows: for presence of carotid plaque 0 = no plaque, 1 = plaque index ≥ 1 ; for severity of carotid plaque 0 = no plaque; 1 = plaque index of 1; 2 = plaque index of 2; 3 = plaque index ≥ 3 . 95% CI = 95% confidence interval (see Table 1 for other definitions).

Table 3. Logistic regression analysis of variables associated with intima-media wall thickness (IMT) in women with systemic lupus erythematosus*

Explanatory variable	Top quartile of IMT		
	Odds ratio	95% CI	P
Age, years	1.15	1.09–1.22	<0.001
Pulse pressure, mm Hg	1.04	1.00–1.09	0.04
Albumin \leq 3.9 gm/dl	7.77	1.30–46.32	0.02
CRP $>$ 4.3 mg/ml	3.01	1.15–7.85	0.02
High cholesterol, yes/no†	2.97	1.18–7.51	0.02
Glucose, mg/dl‡	1.64	1.10–2.43	0.01

* 95% CI = 95% confidence interval (see Table 1 for other definitions).

† High cholesterol defined as having either a fasting total cholesterol level $>$ 220 mg/dl or current use of cholesterol-lowering medication.

‡ Glucose quartiles: 1 = $<$ 90 mg/dl, 2 = 90–95 mg/dl, 3 = 96–104 mg/dl, 4 = $>$ 104 mg/dl.

carotid plaque included older age, higher systolic blood pressure, current antidepressant use, and lower HDL-3 levels (Table 2). Using polychotomous regression, we found that older age, higher systolic blood pressure, lower levels of albumin (defined as \leq 3.9 gm/dl), and having ever smoked were independently associated with a higher plaque index, indicative of more severe plaque.

Intima-media wall thickness. The mean \pm SD IMT of the women in this study was 0.71 ± 0.1 mm. The independent determinants of high IMT, defined as the top quartile of the distribution, included older age, higher pulse pressure, low levels of albumin (defined as \leq 3.9 gm/dl), high CRP levels ($>$ 4.3 mg/ml, mean split), high cholesterol (defined as a fasting total cholesterol $>$ 220 mg/dl or current use of cholesterol-lowering medication), and higher glucose levels (Table 3).

Table 4. Logistic regression analysis of variables associated with pulse-wave velocity (PWV) in women with systemic lupus erythematosus*

Explanatory variable	Top quartile of PWV		
	Odds ratio	95% CI	P
Age, years	1.13	1.07–1.18	<0.001
Systolic blood pressure, mm Hg	1.04	1.01–1.07	0.002
C3, mg/dl	1.02	1.00–1.04	0.03
White cell count, $10^3/\text{mm}^3$	0.83	0.67–1.02	0.07
Insulin, $\mu\text{U}/\text{ml}$ †	1.54	1.05–2.27	0.03
Renal disease‡	7.53	1.84–30.93	0.005

* 95% CI = 95% confidence interval.

† Insulin quartiles: 1 = $<$ 12 $\mu\text{U}/\text{ml}$, 2 = 12–15.4 $\mu\text{U}/\text{ml}$, 3 = 15.5–20.7 $\mu\text{U}/\text{ml}$, 4 = $>$ 20.7 $\mu\text{U}/\text{ml}$.

‡ Renal disease was determined using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index.

Table 5. Logistic regression analysis of variables associated with women at highest risk (n = 23) versus all others (n = 191)*

Explanatory variable	All three outcomes versus others		
	Odds ratio	95% CI	P
Age, years	1.25	1.11–1.41	0.0002
CRP, mg/dl	1.11	0.99–1.24	0.07
Pulse, beats/minute	0.90	0.81–1.01	0.062
Pulse pressure, mm Hg	1.22	1.10–1.36	0.0003
Antidepressant use, yes/no	30.47	4.12–225.61	0.0008
Fibrinogen, mg/dl†	2.29	1.06–4.95	0.034

* Highest risk is defined as having carotid plaque, highest quartile intima-media wall thickness, and highest quartile pulse-wave velocity values. 95% CI = 95% confidence interval (see Table 1 for other definitions).

† Fibrinogen quartiles: 1 = $<$ 257 mg/dl, 2 = 257–293 mg/dl, 3 = 294–333 mg/dl, 4 = \geq 334 mg/dl.

Pulse-wave velocity. The mean \pm SD PWV of the women in this study was 5.96 ± 1.6 meters/second. The risk factors associated with a high PWV, defined as the top quartile of the distribution, included older age, higher systolic blood pressure, higher C3 levels, lower white blood cell count, higher insulin levels, and presence of renal disease (Table 4).

Risk factors associated with women at highest risk. We defined a group of women whom we considered to be potentially at the highest risk of developing a clinical cardiovascular event. These were women with carotid plaque who also had IMT values and PWV values in the highest quartile (n = 23). Using logistic regression modeling, we found that the risk factors associated with the women at highest risk versus the remainder of the women were older age, higher CRP levels, a higher pulse pressure, lower pulse, antidepressant use, and higher fibrinogen levels (Table 5).

DISCUSSION

This is the first study to examine the prevalence and risk factors associated with both anatomic and functional facets of subclinical cardiovascular disease in women with SLE. Because SLE is a systemic disease, subclinical cardiovascular disease may be manifested in different forms and in different vascular beds. By distinguishing atherosclerosis (plaque and IMT) from sclerosis (aortic stiffening), we attempted to identify risk factors specific to these processes. We found that the risk factors associated with subclinical carotid plaque and IMT were, primarily, the traditional cardiovascular risk factors as well as CRP, a marker of inflammation that is now recognized as an important risk factor for cardiovascular disease in the general population. In contrast,

subclinical aortic stiffness was associated with not only the traditional factors but also factors more specific to SLE, such as a low white cell count and elevated levels of C3. These findings are among the results obtained when we examined aortic stiffness in an unselected cohort of women with SLE (5).

A low white cell count is a manifestation of active SLE and may reflect higher disease activity. However, lower C3 levels resulting from complement activation are traditionally associated with higher SLE disease activity. There are several possible explanations for our previous and current observations showing that an elevated C3 level is related to aortic stiffness. First, it may reflect an acute-phase response in which complement acts as an acute-phase reactant and is elevated during inflammation (27). This is unlikely, however, because the other acute-phase reactants we tested, fibrinogen and CRP, were not associated with aortic stiffness in these same patients. Second, vascular pathogenesis may stimulate complement synthesis without complement activation. Third, complement activation may actually contribute to vascular stiffness, but activation is masked by compensatory synthesis of these parent complement proteins. In ongoing studies in our laboratory, we are testing these possibilities.

The systemic nature of SLE may contribute to atherosclerosis by more than one mechanism and may operate at more than one point in the evolution of atherosclerosis. Early in the atherogenic process, mechanisms of SLE related to immune dysregulation and complement metabolism may reduce arterial elasticity, creating an atherogenic milieu. It is thought that reduced elasticity of the arterial walls (sclerosis) may be one of the earliest changes in the development of major vascular disease. Changes to the geometric configuration of vessels may lead to smooth muscle cell hypertrophy and increased collagen. The intimal layer of these stiffened vessels then becomes vulnerable to atherosclerosis and to increased lipoprotein, albumin, and leukocyte permeability (28,29). Thus, an early effect of SLE on vascular stiffening may set the stage for an acceleration of the atherosclerotic process through traditional risk factors. Although our data suggest that SLE may operate in this way, mechanistic studies will be required to establish causality. We considered the possibility that vascular stiffness is reversible in SLE and related to disease activity. However, our observations of the strong and linear association between age and vascular stiffness (Figure 1) would suggest that there is at least a component of vascular stiffness in women with SLE that is irreversible and progresses with age.

Our findings also suggest that mechanisms of SLE related to inflammation may affect vessel wall thickening and the development of plaque. It is now generally believed that inflammation plays an integral role in atherogenesis (30,31), and prolonged exposure to even low levels of acute-phase reactants may cause vascular injury (32) leading to cardiovascular disease. We found that low albumin levels were associated with both focal carotid plaque and high IMT. Albumin is a negative acute-phase reactant, and low serum albumin levels may signal generalized inflammation. Furthermore, an inverse relationship between serum albumin and coronary disease has been identified (33). We also evaluated the potential association between low serum albumin and renal disease, a common SLE condition. The hypoalbuminemia found in the participants of this study was not associated with overt renal disease.

We also observed an association, albeit not statistically significant (at $P < 0.05$) after adjusting for other important factors, between current antidepressant use and the presence of carotid plaque. This is consistent with the findings of a recent study of women at mid-life, which demonstrated that after controlling for biologic and behavioral risk factors for carotid atherosclerosis, a lifetime history of recurrent major depression more than doubled the risk of plaque relative to no history of major depression (34). This relationship between depression and cardiovascular disease may be relevant to lupus patients because they frequently experience depression. Psychosocial factors have been linked to cardiovascular disease, and although antidepressant use is not a psychosocial factor, it may be a marker of depression or anxiety. Chronic psychosocial stress can lead to hypercortisolemia and enhanced platelet function, which are considered proatherogenic (35).

The importance of traditional risk factors should not be overlooked. Our findings that traditional risk factors were associated with all 3 measures of subclinical cardiovascular disease are consistent with our previous findings in women with SLE and the findings of other studies in nonlupus populations (36–41). These factors include older age, high blood pressure, high cholesterol, smoking, and elevated glucose and insulin levels. Many of these factors are modifiable and they should be aggressively treated.

We recognize that our study was limited in that our population consisted predominantly of well-educated white women, which is a reflection of the population in Pittsburgh and the surrounding metropolitan area. Because SLE is prevalent among African American women and other minorities, our results may

not be generalizable to all populations. We also recognize that these results should be interpreted with caution due to our relatively small study sample. This is reflected by wide confidence intervals reported for certain significant risk factors.

In this study of women with SLE without evidence of clinical cardiovascular disease, we found that the risk factors associated with carotid plaque and IMT are those typically associated with cardiovascular disease in the general population. However, SLE-specific variables emerge as important factors in aortic stiffness. Thus, the high prevalence of cardiovascular disease among lupus patients may result from both early adverse effects on vascular stiffening as well as later promotion of wall thickening and plaque through inflammatory-mediated processes. This theory may be supported by our finding of a trend toward an association between longer SLE disease duration and the presence of carotid plaque ($P = 0.09$) and high IMT ($P = 0.07$), but no association with aortic stiffness ($P = 0.18$) (data not shown).

Although cross-sectional observational studies such as the present one cannot determine causality or temporal relationships, they provide valuable information for focusing future studies. Areas for further investigation include determining the process by which lupus-specific factors and inflammatory factors have their effect, and examining the role of immune dysregulation and complement metabolism in arterial stiffness. Such research might lead to potential interventions that may slow or even reverse the progression of atherosclerosis in these women.

ACKNOWLEDGMENT

The authors would like to thank Janice Sabatine, PhD, for editorial assistance and manuscript preparation.

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