Premature Aortic Atherosclerosis in Systemic Lupus Erythematosus: A Controlled Transesophageal Echocardiographic Study

CARLOS A. ROLDAN, JOSEPH JOSON, JANEEN SHARRAR, CLIFFORD R. QUALLS, and WILMER L. SIBBITT, Jr

ABSTRACT. ***Objective.*** Premature carotid and coronary atherosclerosis are common in systemic lupus erythematosus (SLE), but data on aortic atherosclerosis (AA) are limited. Thus, using multiplane transesophageal echocardiography (TEE), we sought to determine the prevalence and clinical correlates of AA in patients with SLE.

Methods. Forty-seven patients with SLE (44 women, age 38 ± 12 years) and 21 healthy controls (19 women, age 34 ± 12 years) underwent clinical and laboratory evaluations and TEE to assess AA defined as aortic intima media thickness (IMT) > 0.86 mm or plaques as > 50% focal IMT as compared with surrounding walls. TEE studies were interpreted by an experienced observer unaware of subjects' clinical data.

Results. The prevalence of abnormal aortic IMT, plaques, or both lesions was higher in patients as compared to controls (37%, 23%, and 43% vs 14%, 0%, and 14%, respectively, all $p \leq 0.02$). In patients, age at diagnosis of SLE was the only positive independent predictor of AA [OR 1.12 per year from diagnosis of SLE, 95% confidence interval (CI) 1.04-1.19, $p = 0.001$] and cyclophosphamide therapy was the only negative independent predictor of AA (OR 0.186, 95% CI 0.153-0.95, $p = 0.04$, equivalent to 5.4 times less likely to develop AA).

Conclusion. AA is common in young patients with SLE and is predicted by a later age at diagnosis of SLE, but is negatively correlated with cyclophosphamide therapy. Thus, early diagnosis and more aggressive immunosuppressive therapy may be required to decrease the development and progression of atherosclerosis in patients with SLE. (J Rheumatol First Release Dec 1 2009; doi:10.3899/jrheum.090665)

Key Indexing Terms:
AORTA ATHEROSCLEROSIS TRANSESOPHAGEAL ECHOCARDIOGRAPHY
SYSTEMIC LUPUS ERYTHEMATOSUS

Cardiovascular and cerebrovascular diseases are common in patients with systemic lupus erythematosus (SLE), a situation that substantially increases their morbidity and mortality[1-4]. Patients with SLE have a higher prevalence of carotid plaques and coronary artery calcifications than matched controls (37% and 31% vs 7–15% and 9%, respectively) after controlling for traditional atherogenic risk factors[5-7]. The SLE-associated immune mediated systemic inflammation is believed to be the primary pathogenic or exacerbating factor for development of atherosclerosis[8-10]. Aortic atherosclerosis (AA) in non-SLE populations is associated with carotid, coronary, and peripheral arterial atherosclerosis, which predicts a 2 to 5-fold increase in future cerebral, cardiac, and peripheral arterial ischemic events and mortality[11-15]. In patients with SLE, AA may have similar clinical and prognostic implications. However, unlike carotid or coronary atherosclerosis, the prevalence of AA in patients with SLE is unknown. Therefore, this study was designed to determine the prevalence and clinical correlates of AA using multiplane transesophageal echocardiography (TEE) in patients with SLE as compared to age- and gender-matched healthy controls.

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Supported by the grant RO1 HLO77422-01-A3 from the National Institutes of Health, NHLBI.

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MATERIALS AND METHODS

Study populations. This study protocol was approved by the Institutional Review Board of the University of New Mexico and conformed to the Declaration of Helsinki. All subjects participated only after signing a written informed consent. Forty-seven consecutive patients with a diagnosis of SLE according to the American Rheumatism Association criteria, 44 of them women, with a mean age of 38 ± 12 years (range, 18-60), and 21 healthy volunteers, 19 of them women, with a mean age of 34 ± 12 years (range, 18-57), agreed to participate in the study. Patients with SLE were recruited from a well-characterized population of ~200 patients between 18

and 60 years old regularly followed at the Rheumatology Clinics of the University of New Mexico Health Sciences Center. Subjects > 60 years old with or without SLE were excluded because of the higher prevalence of atherosclerosis in this age group[16,17].

Clinical and laboratory evaluations. Patients with SLE and controls underwent general clinical and laboratory evaluations including specific measurements of inflammation, coagulation, and fibrinolysis. In addition, patients with SLE were well characterized regarding their demographics; traditional atherogenic risk factors; disease duration, activity, severity, and therapy; standard serology; and antiphospholipid antibody status.

Transesophageal echocardiography. All subjects underwent multiplane TEE with Philips I-E33 systems (Andover, MA) using a 7 MHZ phased array transducer with an axial resolution of 0.1 mm. At a low depth (3-4 cm) and using a narrow sector scan to improve image lateral resolution, 2-dimensional guided M-mode images were used to assess intima media thickness (IMT) and plaques of the anterior wall of the aortic arch and proximal (at 25-30 cm from the incisors), mid (at 30-35 cm), and distal descending thoracic aorta (at 35-40 cm). Also, 2-dimensional images were used to assess aortic IMT and plaques of the medial and lateral walls. Near-field limited resolution precluded accurate assessment of the aortic posterior wall. Also, far-field limited resolution precluded an accurate assessment of IMT of the ascending aorta, but not of plaques. Measurements of IMT were performed from the aortic short and long axis views and during end-diastole after the electrocardiographic P wave. All studies were digitally stored and quantitatively measured off-line using electronic calipers. At each aortic level, 3-6 measurements (from short and long axis views) of the anterior IMT were averaged to determine the mean ± 1SD, minimum, and maximum aortic IMT values. All studies were codified and studies of patients and controls were randomly intermixed and interpreted by an experienced observer unaware of subjects' clinical data.

Criteria for interpretation. In the absence of reported IMT values in healthy subjects, AA was defined as abnormal aortic IMT of > 0.86 mm (value corresponding to the mean in normal controls plus 1.5 SD and which in a receiver-operating curve provided a specificity of 91%) or plaques defined as > 50% focal or protruding wall thickening as compared with surrounding walls[5,18,19] (Figure 1).

Statistical analysis. Student's t test or Wilcoxon rank-sum test (for non-normally distributed data) and Fisher's exact test were used for comparison of continuous and categorical variables among groups, respectively. Univariate and multivariate logistic regression analyses were performed to determine independent effects of clinical and laboratory variables on AA. OR and 95% confidence intervals (CI) were reported. A 2-tailed p value < 0.05 was considered significant.

RESULTS

Characteristics of patients and controls (Table 1). Patients had higher systolic, diastolic, and mean arterial blood pressures, smoked more, had lower hemoglobin, worse renal function and proteinuria, lower albumin, and higher tissue plasminogen activator (tPA) than controls (all $p \leq 0.05$). Other measurements of inflammation, coagulation, and fibrinolysis were similar in patients and controls. Specific clinical, therapeutic, and serologic measurements of SLE are delineated in Table 2.

Aortic IMT and prevalence of AA in patients and controls. Aortic IMT values at the proximal and mid-levels of the descending aorta and arch were significantly higher in patients than in controls (all $p \leq 0.01$, Table 3). The distal descending aorta showed a trend toward significance ($p = 0.07$). Also, the overall mean and maximum IMT values were higher in patients as compared to controls (both $p \leq 0.002$). In both groups, but significantly more in patients with SLE, aortic IMT increased with age (Figure 2). Of most importance, the overall prevalence of abnormal aortic IMT, plaques, or both lesions was higher in patients than in controls (37%, 23%, and 43% vs 14%, 0%, and 14%, respectively, all $p \leq 0.02$, Table 3).

Predictors of aortic atherosclerosis in patients and controls. In multivariate analyses that included all demographic, clinical, and laboratory variables delineated in Table 1, only age and SLE disease were independent predictors of AA (OR 1.08 per year of age increment, 95% CI 1.025 to 1.4, $p = 0.004$; and OR 6.7 for the SLE group, 95% CI 1.28 to 35, and $p = 0.02$; Figure 2).

Predictors of AA in patients with SLE (Table 4). In univariate analyses that included all variables delineated in Tables 1 and 2, only age and age at diagnosis of SLE were positive predictors of AA (OR 1.08 per year of age, CI 1.02 to 1.14, $p = 0.009$, and OR 1.12 per year from age at diagnosis of SLE, CI 1.04 to 1.19, $p = 0.001$). Cyclophosphamide therapy was a negative predictor of AA (OR 0.172, CI 0.045 to 0.655, $p = 0.01$, equivalent to 5.8 times less likely to develop AA). In multivariate analyses, only age at diagnosis of SLE and cyclophosphamide therapy were independent predictors of AA (OR = 1.12 per year from age at diagnosis of SLE, 95% CI 1.043 to 1.2, $p = 0.001$ and OR 0.19, 95% CI 0.15 to 0.95, $p = 0.04$, equivalent to 5.4 times less likely to develop AA on cyclophosphamide therapy; Figure 3).

DISCUSSION

There are 3 major findings in this study: (1) aortic IMT values in patients with SLE are higher than in gender- and age-matched controls; (2) the prevalence of AA is also higher in patients with SLE than in matched controls; and (3) age at diagnosis of SLE is the strongest independent positive predictor and cyclophosphamide therapy the independent negative predictor of AA. Therefore, SLE-associated chronic immune-mediated inflammation is an important independent primary or a potentiating pathogenic factor on age and traditional atherogenic risk factors for development or progression of atherosclerosis[3,5,7-9,20-22]. Other series have demonstrated equivalent prevalence of subclinical carotid and coronary atherosclerosis in SLE[3,5,7]. In this study, the later the age at diagnosis of SLE, the higher the likelihood of developing AA. In contrast, cyclophosphamide therapy had a protective effect. These findings emphasize the importance of inflammation in the pathogenesis of AA and the need for an early diagnosis and aggressive treatment of SLE[5,6,23].

In our study, the lack of an independent association of other specific SLE measurements of inflammation with AA may be explained by 2 factors. First, this SLE cohort was aggressively treated with cyclophosphamide and/or antimetabolites when inflammation was present rather than

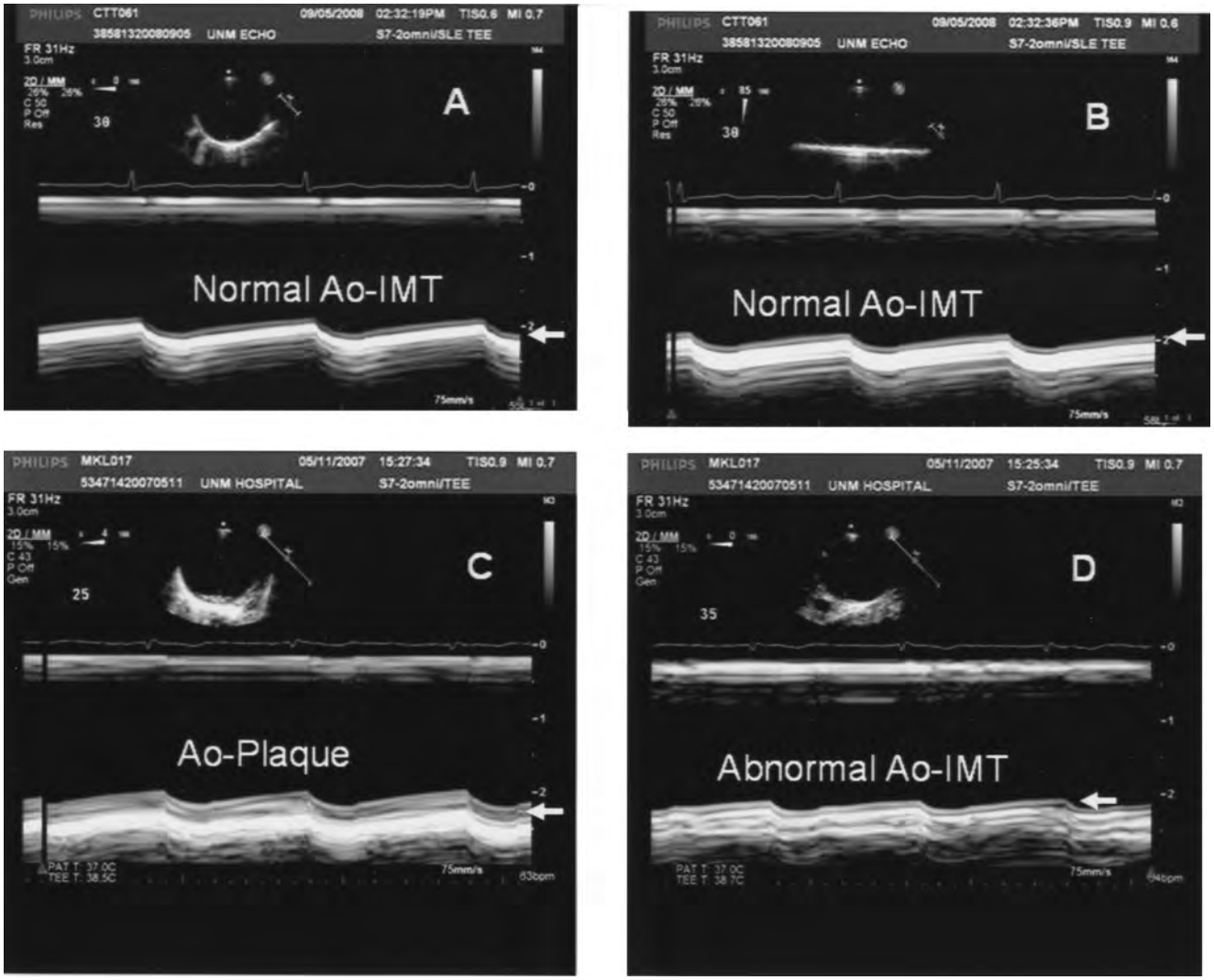

Figure 1. Aortic Intima-Media Thickening and Plaques by TEE. Short axis (A) and long axis (B) 2-dimensional guided M-mode images of the anterior wall at the mid-level (30 cm) of the descending thoracic aorta demonstrating normal intima media thickness (IMT) of < 8 mm (arrows) in a 50-year-old woman with SLE. C, D. 2-dimensional guided M-mode images of a 48-year-old woman with SLE demonstrating a well-defined aortic plaque of 3.3 mm at the proximal (C, arrow) and abnormal IMT of 1.2 mm at the distal (D, arrow) descending thoracic aorta.

relying on antimalarials and corticosteroids. Second, inflammation in SLE is variable over time and atherosclerosis likely results from the cumulative effects of inflammation over many years, thus, more aggressive and prolonged noncorticosteroid immunosuppression may have more effective antiatherogenic influence than traditional time-delimited approaches. Also in our study, traditional atherogenic risk factors were not statistically independent predictors of AA. However, these factors likely have an important exacerbating biologic effect on immune-mediated inflammation in the pathogenesis or progression of AA in SLE[5,6,24].

In non-SLE populations, a strong association has been demonstrated between moderate to severe degrees of AA (IMT > 4 mm or protruding atheromas) and coronary and cerebrovascular disease [11-15]. In these series, AA has shown to be a marker of generalized atherosclerosis and a predictor of a 2-5 fold increased risk of future acute coronary syndromes, stroke or transient ischemic attacks, and cardiac or cerebrovascular mortality. In addition, AA has been proposed to be a substrate for cerebral and peripheral atheroemboli. Thus, AA exacerbated by hypercoagulability in patients with SLE may not only be a marker of coronary and cerebral atherosclerosis, but also a pathogenic factor for cardiac, cerebral, and peripheral arterial thrombotic or thromboembolic ischemic events. In fact, some series in SLE have reported the association of AA with aortic aneurysms or peripheral arterial disease with claudication or ischemic events requiring amputation of digits or extremities[25-28].

Comparison with previous studies. No prior study was found in the literature assessing AA in patients with SLE.

Table 1. Clinical and laboratory data in patients with SLE and controls.

Characteristic	Patients, n = 47	Controls, n = 21	p
Age, yrs	38 ± 12 (18–60)	34 ± 12 (18–57)	0.17
Female, %	94	90	0.64
Nonhispanic whites and Hispanic, %	36 and 55	38 and 48	0.81
Body mass index, kg/m^2	27 ± 6	26 ± 5	0.41
Systolic blood pressure, mm Hg	125 ± 14	117 ± 9	0.008
Diastolic blood pressure, mm Hg	77 ± 10	73 ± 6	0.05
Mean arterial blood pressure, mm Hg	93 ± 10	88 ± 6	0.01
Smoking*, %	53	24	0.03
Hemoglobin, g/dl	13.3 ± 1.6	14 ± 1.5	0.04
Platelets, k/mm^3	251 ± 96.7	268 ± 41	0.36
White blood cell count, k/mm^3	5.6 ± 2.2	6.5 ± 1.8	0.08
Cholesterol, mg/dl	184 ± 45	185 ± 45	0.95
Triglycerides, mg/dl	153 ± 78	156 ± 103	0.91
Creatinine, mg/dl	0.83 ± 0.33	0.73 ± 0.11	0.05
Proteinuria, mg/dl	50 ± 117	3.5 ± 8	0.01
Glucose, mg/dl	90 ± 21	82.6 ± 9	0.13
Albumin, g/dl	3.9 ± 0.6	4.3 ± 0.3	0.007
P-selectine, ng/ml	42 ± 20.45	39 ± 16	0.49
C3a, pg/ml	2301 ± 3317	2096 ± 2218	0.77
C5a, pg/ml	31.6 ± 10.7	29 ± 9.8	0.37
Quantitative D-dimer, μg/ml	1.01 ± 3.2	0.33 ± 0.39	0.17
tPA, ng/ml	10.3 ± 6.6	7.6 ± 4.4	0.05
PAI-1, U/ml	9.7 ± 12.5	17.3 ± 37	0.36
Peak thrombin generation, nmol/l	390.8 + 133.5	440 ± 136.5	0.19
Thrombin-antithrombin complexes, ng/ml	7.5 ± 10	5.8 ± 7	0.45
Platelet-derived CD41 microparticles, μl	552.9 ± 668	517 ± 592	0.83
Monocyte-derived CD41 microparticles, μl	441.7 ± 668	476.7 ± 486.6	0.81
Endothelium-derived CD144 microparticles, μl	161.6 ± 235	154 ± 122	0.87

* Defined as any amount of smoking for any duration of time. tPA: tissue plasminogen antigen; PAI: plasminogen activator inhibitor.

However, the 43% prevalence of AA found in this study is similar to the reported rates of carotid plaques by ultrasonography (37.1%) and coronary artery calcification (31%) by electron beam computed tomography[5,6]. Also in these and other series, SLE was an independent predictor of atherosclerosis (OR 6.7, CI 1.28 to 35, p = 0.02), patients with atherosclerosis were diagnosed at a later time, and cyclophosphamide therapy had a protective effect[29-31]. In addition, as in other series, specific markers of inflammation and antiphospholipid antibodies were not temporally associated with AA. In contrast to previous series, our patient population was younger (mean age 38 ± 12 years) and therefore the observable effects of aging, longterm hyperlipidemia, and of other traditional risk factors for atherosclerosis were reduced.

Pathogenesis of atherosclerosis in SLE. The following interrelated mechanisms lead to the development of atherosclerosis in patients with SLE[5,8-10,20-22,24,32,33]: (1) active cellular and humoral immunity result in activation of macrophages, lymphocytes, phagocytes, and neutrophils, CD4+CD28– and CD36 T-cells, and dendritic cells; these cytotoxic cells (either circulating or endovascularly adhered) cause platelets to release platelet-derived growth factors and thromboxane A^2 (a vasoconstrictor and platelet activator) and a decrease in endothelial cells' production of nitric oxide and prostacyclin, all resulting in vasoconstriction and/or thrombosis; (2) cytotoxic cells also produce multiple cytokines (granulocyte or monocyte colony-stimulating factors, interferon-α, ß, or γ, interleukins, tumor necrosis factor-α or ß, and macrophage migration inhibition factor), that are proinflammatory and chemotactic and increase proliferation of smooth muscle cells, and further activate macrophages with release of free radicals, matrix metalloproteinases, and elastase, causing elastin degradation and release of fibroblast growth factors; (3) mononuclear and endothelial cell activation increased production of chemokines (heat shock proteins, C-reactive protein, rheumatoid factor), which recruit inflammatory cells, upregulate endothelial production of vascular and intercellular adhesion molecules, which further promote adhesion of inflammatory cells, vascular smooth-muscle cell proliferation, oxidative stress, endothelial dysfunction and apoptosis, extracellular matrix and collagen deposition; (4) endothelial dysfunction increased production of proinflammatory high-density lipoproteins, oxidative low-density lipoproteins, and activation of the renin-angiotensin system; and (5) SLE disease or steroid therapy-related hypertriglyceridemia, hypercholesterolemia, homo-

Table 2. Clinical and laboratory data in patients with SLE.

Characteristic	Patients n = 47, mean ± SD, (%)
Duration of SLE, yrs	8.9 ± 7.3 (range 1–31)
Age at diagnosis of SLE, yrs	29.5 ± 12.6 (range 10–56)
Smoking (≥ 10 pk/yrs), %	30
Hypertension (SBP ≥ 140 and DBP ≥ 90 mm Hg, %	16
Diabetes mellitus (fasting glucose > 130 mg/dl or on therapy), %	4
Hyperlipidemia (cholesterol ≥ 240 or triglycerides > 150 mg/dl), %	45
Any atherosclerotic risk factor, %	70
Postmenopausal status, %	9
Total SLEDAI	12 ± 10.4 (range, 1–47)
Total SLICC	3.3 ± 2.4
Prednisone therapy, %	87
Prednisone average dose, mg/day	7.5 ± 7.3 (range, 0–40)
Prednisone, yrs	7.2 ± 6.7 (range, 0–30)
Cyclophosphamide therapy, %	30
Years of cyclophosphamide therapy	0.64 ± 0.90 (range 0–3)
Mycophenalate or methotrexate therapy, %	17
Hydroxychloroquine or chloroquine therapy, %	47
Aspirin, warfarin, or clopidogrel, %	21
DNA titer (dilutions)	31.6 ± 50
ANA titer (dilutions)	353 ± 447
Antiphospholipid antibody-positive, %	57
IgM anticardiolipin antibody, IU	9.3 ± 15
IgG anticardiolipin antibody, IU	12.6 ± 19
IgA anticardiolipin antibody, IU	5.9 ± 11.7
Smith antibody-positive, %	30
SSA antibody-positive, %	40
C3, mg/dl	99.4 ± 3.6
C4, mg/dl	20.8 ± 25.3
CH50, mg/dl	84.4 ± 36.4
C-reactive protein, mg/dl	1.13 ± 1.5
Erythrocyte sedimentation rate, mm/h	24.6 ± 25.7

Data presented as mean ± SD. SLEDAI: SLE disease activity index; SLICC: SLE International Collaborating Clinics Damage Index; ANA: antinuclear antibody.

cysteinemia, and insulin resistance. These pathogenetic mechanisms result in endothelial dysfunction and apoptosis, smooth muscle cells proliferation, aortic wall hypertrophy and fibrosis, aortic stiffness, increase in arterial impedance, and ultimately in atherosclerosis.

Limitations: (1) our patient population represents about 30% of ~200 potentially eligible patients from a tertiary care center. Thus, the prevalence of AA found in this study may be an over- or underestimation as compared to that of a general SLE population; (2) limited visualization of the aortic posterior wall by TEE may have led to underestimation of AA; (3) our age- and gender-matched healthy control group was small and therefore may have contributed to an overestimation of the independent effect of SLE on AA; and (4) the cutoff value of 0.87 mm used for defining abnormal IMT may have caused an overestimation of AA. However, the prevalence of AA using a cutoff of > 1 mm showed similar prevalence of abnormal IMT (34% vs 10%, p = 0.04) and an overall similar prevalence of AA among groups (36% vs 10%, p = 0.04; Figure 4).

Clinical implications of the study: (1) SLE-associated chronic immune-mediated inflammation may promote premature large-vessel atherosclerosis as it does for medium-size carotid and coronary atherosclerosis; (2) an earlier diagnosis and aggressive antiinflammatory therapy of SLE using noncorticosteroid immunosuppressives may prevent the development and progression of atherosclerosis; (3) AA may play a pathogenic role in peripheral arterial thrombotic or thromboembolic ischemic disease in SLE; (4) subclinical AA may exacerbate aortic stiffness, hypertension, and increased left ventricular mass and diastolic dysfunction in SLE[34-36]; and (5) antiplatelet and statin therapy may have primary and secondary protective effects in SLE[37,38]. These diagnostic and therapeutic interventions may decrease the current 2- to 3-fold increased morbidity and mortality of patients with SLE with coronary, cerebrovascular, or peripheral arterial disease. However, a larger cross-sectional and longitudinal study is necessary to better define the short-term and longterm clinical, therapeutic, and prognostic implications of AA in SLE.

Table 3. Aortic intima-media thickness (IMT), abnormal intima-media thickening, and plaques in patients with SLE and controls.

	Patients (n = 47)	Controls (n = 21)	p
	IMT (mm), mean (minimum, maximum)		
Aortic level (anterior wall)			
Distal (35–40 cm)	0.83 ± 0.34 (0.47, 2.35)	0.71 ± 0.17 (0.47, 1.23)	0.07
Mid (30–35 cm)	0.95 ± 0.66 (0.47, 4.23)	0.67 ± 0.20 (0.47, 1.3)	0.01
Proximal (25–30 cm)	0.82 ± 0.27 (0.47, 1.57)	0.66 ± 0.19 (0.47, 1.27)	0.01
Arch	0.86 ± 0.29 (0.53, 1.83)	0.65 ± 0.12 (0.40, 0.93)	0.001
Overall aortic IMT (maximum)	1.11 ± 0.68 (0.57, 4.23)	0.76 ± 0.19 (0.55, 1.30)	0.002
Overall aortic IMT (mean)	0.86 ± 0.27 (0.51, 1.89)	0.67 ± 0.15 (0.49, 1.13)	0.001
Aorta IMT (%)			
Distal (35–40 cm)	15/46 (33)	3 (14)	0.15
Mid (30–35 cm)	17/46 (37)	3 (14)	0.09
Proximal (25–30 cm)	15/46 (33)	3 (14)	0.14
Arch	13/34 (38)	1/19 (5)	0.01
Any aortic portion	17 (37)	3 (14)	0.02
Aortic plaque (%)			
Distal (35–40 cm)	4/43 (9)	0/20	0.21
Mid (30–35 cm)	4/42 (10)	0/20	0.39
Proximal (25–30 cm)	4/42 (10)	0/20	0.39
Arch	6/44 (14)	0	0.17
Ascending aorta	1/47 (2)	0	1.0
Any aortic portion	11 (23)	0	0.01
Aortic IMT or plaque (%)			
Any aortic portion	20 (43)	3 (14)	0.02

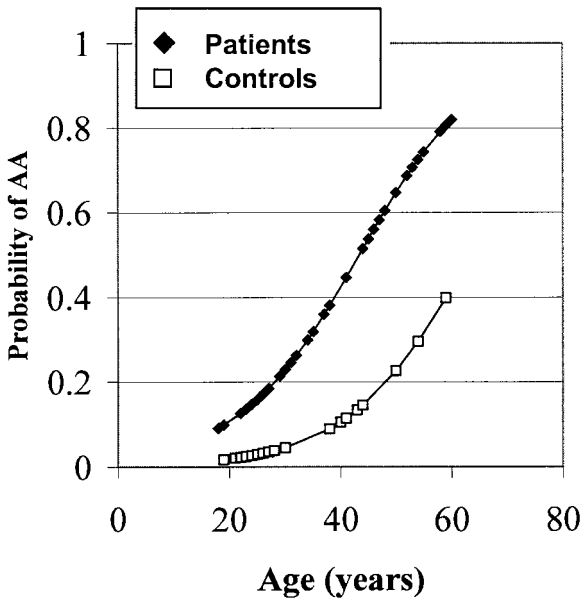

Figure 2. Aortic atherosclerosis (AA) vs age by group. By multivariate analyses, age and SLE disease were the only independent predictors of AA [OR 1.08 per year of age increment, 95% confidence interval (CI) 1.025-1.4, p = 0.004 for age effect; and OR 6.7, CI 1.28-35, and p = 0.02, for group (SLE) effect]. The probability of AA in patients with SLE was 40% at age 40 and 80% at age 60 as compared to 10% and 40%, respectively, in controls.

Table 4. Predictors of aortic intima-media thickening or plaques in patients with SLE.

Variable	Odds Ratio	95% CI	p
Univariate analyses			
Age	1.08 per year	1.020–1.14	0.009
Age at diagnosis of SLE	1.12 per year	1.04–1.19	0.001
Cyclophosphamide therapy	0.17	0.045–0.655	0.01
Multivariate analyses			
Age at diagnosis of SLE	1.12 per year	1.037–1.21	0.001
Cyclophosphamide therapy	0.19	0.153–0.95	0.03

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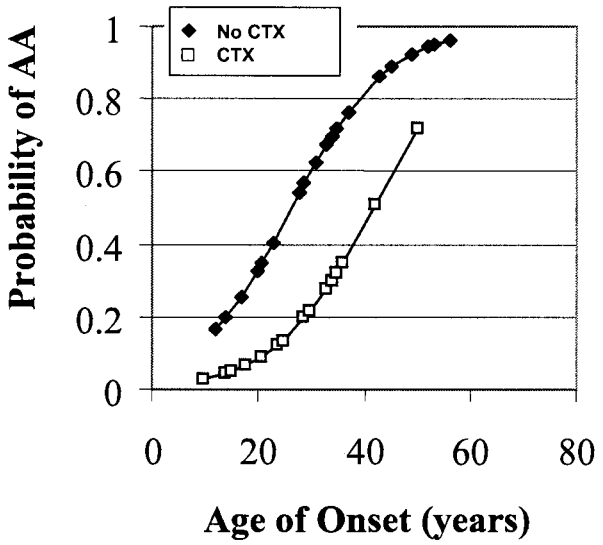

Figure 3. Aortic atherosclerosis vs age at diagnosis of SLE by cyclophosphamide therapy. In patients with SLE and by multivariate analyses, age at diagnosis of SLE was the only independent positive predictor and cyclophosphamide (CTX) therapy was the only independent negative predictor of AA (OR = 1.118 per year from diagnosis of SLE, 95% CI 1.037-1.2, p = 0.004 and OR 0.186, CI 0.039-0.875, p = 0.03, equivalent to 5.4 times less likely to develop AA). Probabilities of AA in patients with no cyclophosphamide therapy were nearly 40% at age 20, 80% at age 40, and almost 100% at age 60 as compared to nearly 10% at age 20, 40% at age 40, and 70% at nearly age 60 in patients on cyclophosphamide therapy.

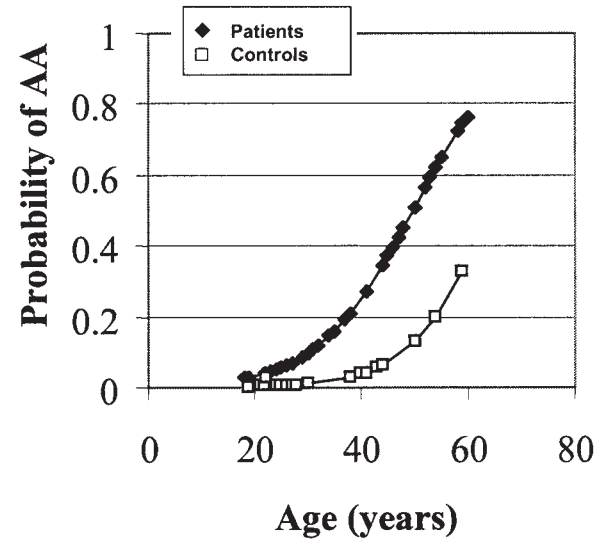

Figure 4. Aortic atherosclerosis defined as intima media thickening > 1 mm or plaques vs age by group. By multivariate analyses, age and SLE disease were the only independent predictors of AA [OR 1.08 per year of age increment, 95% confidence interval (CI) 1.025-1.4, p = 0.005 for age effect; and OR 6.7, CI 1.28-35, and p = 0.03, for group (SLE) effect]. Note that the probability of AA in patients with SLE was 40% at age 40 and 75% at age 60 as compared to 5% and nearly 35%, respectively, in controls.

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