Novel Cardiovascular Risk Factors in Premature Coronary Atherosclerosis Associated with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Several mediators of inflammation are associated with atherosclerotic cardiovascular disease in the general population, but their relationship to accelerated atherosclerosis associated with an inflammatory disease such as systemic lupus erythematosus (SLE) is not known.

Methods. We compared concentrations of cytokines (TNF-α, IL-1α, and VEGF), inflammatory enzymes (MPO and MMP-9), acute-phase reactants (ESR, CRP, and SAA) and adhesion molecules (VCAM, ICAM, and E-selectin) in 109 patients with SLE and 78 controls. The relationship between inflammatory markers and coronary atherosclerosis detected as calcified plaque by electron beam CT was determined in patients with SLE.

Results. Concentrations of all markers of inflammation other than VCAM, MMP-9, and IL-1α were significantly higher in SLE. In multivariable analyses adjusting for Framingham risk score, cumulative corticosteroid dose, and diabetes, E-selectin (OR 1.90, 95% CI 1.08–3.33), VCAM (OR 1.99, 1.18–3.37), ICAM (OR 2.30, 1.13–4.7), and TNF-α (OR 2.36, 1.10–5.06) were significantly associated with the severity of coronary calcium.

Conclusion. Concentrations of adhesion molecules and TNF-α are associated with coronary atherosclerosis in SLE independent of the Framingham risk score. (First Release July 15 2008; J Rheumatol 2008;35:1789–94)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS ATHEROSCLEROSIS
CELL ADHESION MOLECULE TUMOR NECROSIS FACTOR-α CYTOKINES

Atherosclerosis is the major pathophysiologic mechanism underlying ischemic cardiovascular disease; it is not merely a passive degenerative process, but rather a process initiated and facilitated by inflammation[1]. Systemic lupus erythematosus (SLE) is an autoimmune disease that involves multiple organs and is characterized by persistent systemic inflammation. Patients with chronic inflammatory diseases such as SLE develop atherosclerosis prematurely[2-4], and this is not accounted for by an increased prevalence of traditional cardiovascular risk factors such as dyslipidemia and hypertension, characterized by the Framingham risk score[5,6]. Thus, inflammation has been suggested as a mechanism mediating the accelerated atherosclerosis observed in SLE. The recognition that inflammation is important in the pathogenesis of atherosclerosis came from pathological studies[7], animal models[8], and the realization that acute-phase markers such as C-reactive protein (CRP)[9] were independently associated with the risk of future cardiovascular events. In addition to CRP, several other markers or mediators of inflammation have been associated with atherosclerosis or cardiovascular risk. These include tumor necrosis factor-α (TNF-α)[10], interleukin 1α (IL-1α), vascular endothelial growth factor (VEGF)[11], myeloperoxidase (MPO)[12], matrix metalloproteinase-9 (MMP-9)[13], serum amyloid A (SAA)[14], vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and E-selectin[15,16].

The molecular basis of inflammation in the pathogenesis of atherosclerosis in SLE has not been studied extensively. Large prospective cohort studies that examine the relationship between inflammatory markers and cardiovascular outcomes such as myocardial infarction are not feasible, given the relative rarity of SLE. However, the ability to detect and quantify coronary atherosclerosis noninvasively through the

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measurement of coronary calcium by electron beam computed tomography (EBCT) can provide valuable insights into the mechanisms underlying accelerated atherosclerosis.

We previously reported that both the prevalence and severity of coronary artery calcium detected by EBCT were increased in patients with SLE[3] and that concentrations of IL-6 were increased and associated with coronary calcification[17]. Our present study extends that work to address the role of other cytokines, inflammatory enzymes, acute-phase reactants, and adhesion molecules that have been associated with cardiovascular disease or atherosclerosis in the general population[9,15]. Thus, we addressed the hypothesis that concentration of cytokines (TNF-α, IL-1α, and VEGF), inflammatory enzymes (MPO and MMP-9), acute-phase reactants [erythrocyte sedimentation rate (ESR), CRP, SAA], and adhesion molecules (VCAM, ICAM, E-selectin) are increased in SLE and contribute to the pathogenesis of accelerated atherosclerosis.

MATERIALS AND METHODS

Patients. This was a cross-sectional study of 187 subjects (109 patients with SLE and 78 control subjects). Patients were older than 18 years and fulfilled the 1997 American College of Rheumatology (ACR) classification criteria for SLE[18] for at least 1 year; control subjects did not meet classification criteria for any rheumatic disease. Subjects with a history of angina, acute myocardial infarction, or stroke were excluded. The subjects represent a cohort that has been studied to determine the relationship between inflammation and atherosclerosis, and the methods used have been described[3,6,17,19]. The study was approved by the Vanderbilt Institutional Board of Review, and all subjects gave written informed consent.

Clinical assessment. Each subject was evaluated clinically through a structured interview, physical examination, medical chart review, and laboratory assessment. Disease activity indices such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[20] and Systemic Lupus International Collaborating Clinics / American College of Rheumatology damage index (SLICC/ACR Damage Index)[21], and a drug history that included cumulative corticosteroid dosage were obtained in patients with SLE. All subjects underwent coronary calcium measurement through EBCT scanning as described[3], and the degree of calcification was quantified as described by Agatston, *et al*[22].

Laboratory assessment. Whole blood was drawn by venipuncture for determination of a complete blood count, serum creatinine, glucose, triglycerides, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol concentrations. Erythrocyte sedimentation rate (ESR) and CRP were determined in patients only by the Vanderbilt University Hospital clinical laboratory. Assays for cytokines, adhesion molecules, and inflammatory enzymes associated with atherosclerosis were performed using the Lincoplex® Multiplex Immunoassay Kit (Linco Research, St. Charles, MO, USA). The following inflammatory mediators were measured: E-selectin, VCAM, ICAM, TNF-α, VEGF, MMP-9, MPO, SAA, and IL-1α.

Statistical analysis. Clinical characteristics were described as mean ± standard deviation (SD) and inflammatory mediators as median with interquartile range (IQR). Concentrations of inflammatory mediators were compared between patients with SLE and control subjects using Wilcoxon rank-sum tests. The correlation between inflammatory mediators and clinical variables as well as coronary calcium severity was assessed in patients with SLE using Spearman's rank correlation coefficient (rho) and its corresponding test. To assess independent effects of each marker of inflammation on the severity of coronary calcification in patients with SLE, proportional odds logistic regression models were used to adjust for traditional cardiovascular risk factors as determined by the Framingham risk score[23], the presence of diabetes, and cumulative corticosteroid dose. Additional models were applied to further examine the relationship between inflammatory mediators and coronary calcium. To preserve regression power, and avoid multicollinearity by including multiple correlated variables, we combined ICAM, VCAM, and E-selectin into a single component variable ("adhesion molecules"), and similarly ESR and CRP into a single component ("inflammatory markers") via principal components analysis[24]. Inflammation markers were logarithm-transformed to achieve normal distribution and improve model goodness of fit.

Statistical analysis was performed with R 2.4.0 (http://www.r-project.org) and a 2-sided 5% significance level was considered significant. The authors had full access to the data.

RESULTS

Clinical data and markers of inflammation. Demographic and clinical characteristics of patients with SLE and control subjects are shown in Table 1. The study population comprised predominantly middle-aged women (~90%) with a similar proportion in both patient and control groups. As reported[3], patients with SLE were more often hypertensive, had higher levels of serum triglycerides, and higher coronary calcium scores (Table 1). The concentrations of inflammatory markers are shown in Table 2. Levels of E-selectin, ICAM, MPO, SAA, VEGF, and TNF-α were significantly higher in patients with SLE than controls (all $p < 0.05$).

Markers of inflammation in patients with SLE. Measures of disease activity (SLEDAI) and damage (SLICC) did not correlate strongly with inflammatory markers; SLEDAI was significantly correlated with ESR and CRP (rho = 0.21 and 0.19), and SLICC with E-selectin (rho = 0.19). The Framingham score was significantly correlated with acute-phase reactants (CRP rho = 0.23, SAA rho = 0.25) and age (rho = 0.73), which is a component of the score (all p <

Table 1. Clinical characteristics in patients with SLE and control subjects. Data are presented as mean ± SD or percentages.

Factor	Controls, n = 78	SLE, n = 109	p*
Age, yrs	40.5 ± 12.0	40.2 ± 11.5	0.863
Female, %	85.9	91.7	0.202
BMI, kg/m^2	26.99 ± 6.0	29.18 ± 7.49	0.049
Hypertension, %	16.7	45.0	< 0.001
Diabetes, %	1.3	4.6	0.206
Smoker, %	17.9	26.6	0.165
Systolic BP, mm Hg	117.2 ± 14.0	119.7 ± 17.3	0.499
Diastolic BP, mm Hg	71.0 ± 10.0	73.9 ± 13.6	0.226
Glucose, mg/dl	85.8 ± 9.5	86.9 ± 26.0	0.207
Cholesterol, mg/dl	179.5 ± 42.0	175.1 ± 47.1	0.182
HDL, mg/dl	49.1 ± 15.6	47.2 ± 14.8	0.564
LDL, mg/dl	111.1 ± 34.9	104.0 ± 38.2	0.058
Triglycerides, mg/dl	97.1 ± 55.9	119.1 ± 58.6	0.003
Framingham score	5.2 ± 7.5	6.0 ± 6.3	0.467
Agatson score	3.87 ± 28.3	43.12 ± 192.6	0.002

BMI: body mass index. BP: blood pressure. * Wilcoxon rank-sum test, percentages used chi-square test.

Table 2. Concentrations of inflammatory markers and mediators in patients with SLE and control subjects.

Marker	Controls, Median (IQR)	SLE, Median (IQR)	p*
E-selectin, ng/ml	18.4 (14.0–22.9)	23.9 (17.7–28.6)	< 0.001
VCAM, ng/ml	1016.8 (836.8–1116.5)	1077.4 (887.9–1203.3)	0.09
ICAM, ng/ml	144.4 (120.8–179.4)	175.4 (135.1–226.5)	0.001
MPO, ng/ml	20.0 (11.2–29.0)	25.0 (15.0–45.7)	0.02
MMP-9, ng/ml	89.8 (59.2–140.3)	81.5 (55.6–129.1)	0.38
SAA, µg/ml	1.2 (0.6–2.4)	2.5 (1.2–6.1)	< 0.001
ESR, mm/h	—	17 (9–35)	—
CRP, mg/l	—	4.0 (0.6–7)	—
TNF-α, pg/ml	2.4 (1.9–3.1)	4.8 (3.0–7.9)	< 0.001
IL-1α, pg/ml	128.3 (18.7–414.6)	120.7 (13.9–672.8)	0.83
VEGF, pg/ml	30.8 (7.5–77.1)	40.0 (18.2–81.7)	0.04

* Wilcoxon rank-sum test. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ICAM: intercellular adhesion molecule; IL-1α: interleukin 1α; IQR: interquartile range; MMP-9: matrix metalloproteinase-9; SAA: serum amyloid A; TNF-α: tumor necrosis factor-α; VCAM: vascular cell adhesion molecule; VEGF: vascular endothelial growth factor.

0.05). There was no significant association between the adhesion molecules and cumulative steroid dosage (p values all > 0.05). Further, concentrations of ICAM (p = 0.89), VCAM (p = 0.41), and E-selectin (p = 0.26) were similar in subjects currently receiving corticosteroids and those who were not.

Relationship between clinical and inflammatory measures and coronary artery calcium in patients with SLE. The relationships between markers of inflammation and coronary calcium are shown in Figure 1. Spearman correlations indicated that E-selectin, VCAM, ICAM, SAA, and CRP were significantly associated with coronary calcium (p < 0.05). TNF-α and the adhesion molecules E-selectin, VCAM, and ICAM were independently associated with the severity of coronary calcium adjusted for covariates (Framingham risk score, diabetes, and cumulative corticosteroid exposure). In addition, to further examine the relationship between inflammatory mediators and coronary calcium we applied additional models by combining multiple correlated variables, ICAM, VCAM, and E-selectin into a single component variable (adhesion molecule), and similarly ESR and CRP into a single component (inflammatory markers) via principal components analysis. The components of adhesion molecules and inflammatory markers contained 60% and 67% of the variation in each set of original variables, respectively. The effect of TNF-α adjusted for Framingham risk score, diabetes, and cumulative corticosteroid dose (p = 0.027) was attenuated by further adjustment for the adhesion molecules and inflammation marker components (TNF-α p = 0.20). In this model, the effect of the adhesion molecules component was statistically significant (p = 0.015), whereas that of inflammation markers was not (p = 0.872).

DISCUSSION

This is the first study to report the relationships between several inflammatory mediators implicated in the pathogenesis of accelerated atherosclerosis and coronary calcification in patients with SLE. The major finding of this study, i.e., that the adhesion molecules VCAM, ICAM, E-selectin, and the cytokine TNF-α are associated with subclinical atherosclerosis in patients with SLE independent of Framingham risk score, provides new insights into mechanisms that may contribute to accelerated atherosclerosis associated with inflammation.

Although substantial evidence links mediators of inflammation with atherosclerosis in the general population, there is little information about this relationship in patients with SLE, a group recently recognized to have accelerated atherosclerosis[3,4]. One reason for lack of information about the relationship between mediators of inflammation and atherosclerosis in SLE is that it is difficult to perform large prospective studies of cardiovascular events because the disease is relatively uncommon. Recently, the ability to noninvasively and accurately quantify the atherosclerotic burden in the coronary arteries using EBCT, and the recognition that coronary calcium is a strong predictor of risk of cardiovascular events, have provided a means for examining the burden of atherosclerosis, and its potential causes, in SLE[25].

The accelerated atherosclerosis associated with SLE is thought to be related to inflammation, but few studies have addressed this question, and there is little information relevant to the development of coronary atherosclerosis. Most studies used carotid ultrasound to detect atherosclerotic plaque in SLE. Antibodies to oxidized LDL[26], anti-oxPAPC (oxidized palmitoyl arachidonoyl phosphocholine) antibodies[27], transforming growth factor-$ß_1$[28], and antiphospholipid antibodies[29] have been associated with carotid atherosclerosis. Coronary calcification has been associated with asymmetric dimethylarginine (ADMA)[30] and high C3 concentrations[31] in SLE. Our study provides information about several inflammatory cardiovascular risk factors, some evaluated for the first time, in coronary atherosclerosis associated with SLE.

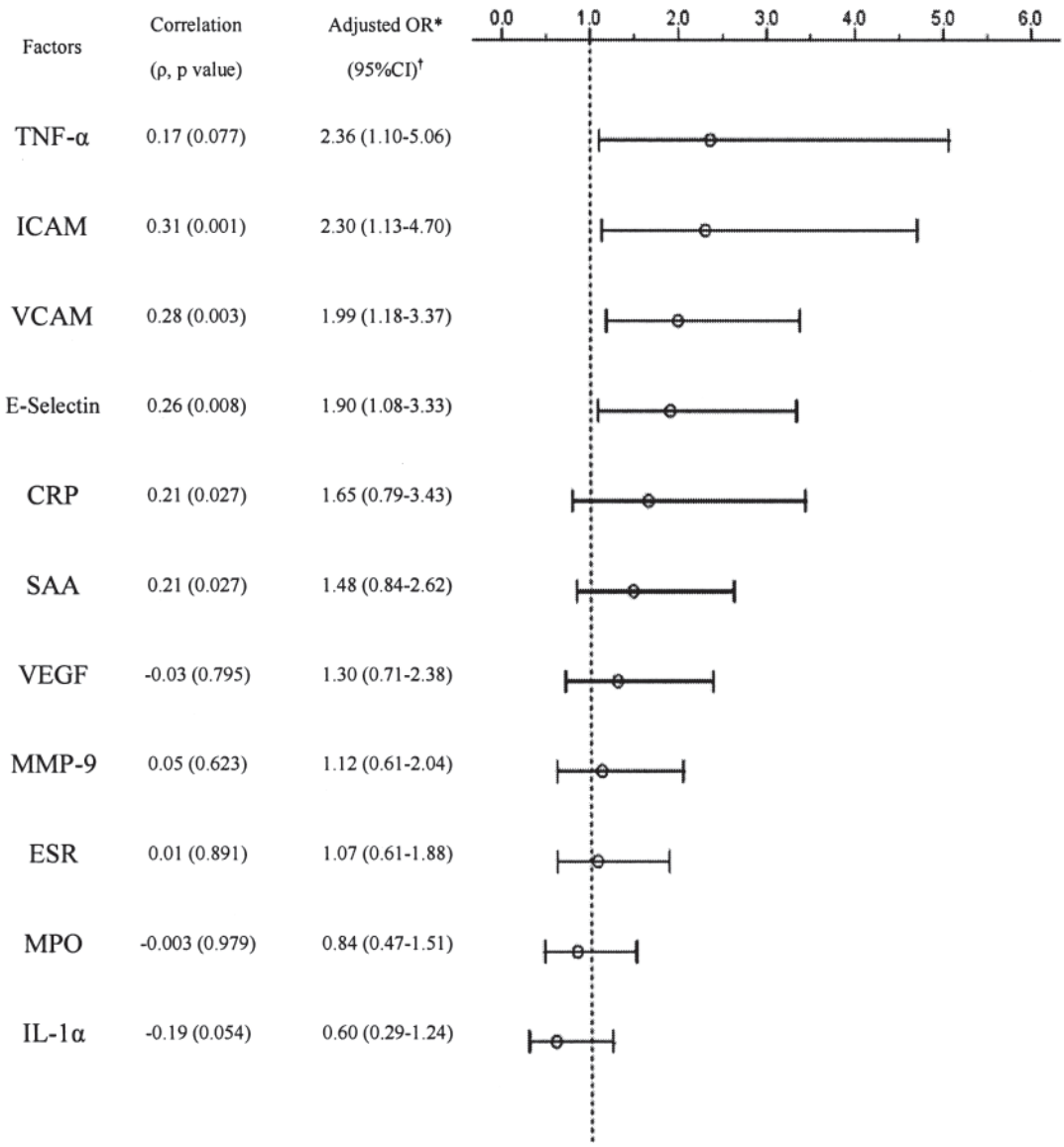

Figure 1. Univariate Spearman correlation coefficients and adjusted odds ratios (OR) for the outcome of coronary calcification severity by cardiovascular and inflammatory mediators. *Proportional odds model was used to calculate OR for increasing coronary calcification severity (n = 107). †Models were adjusted for Framingham risk score, cumulative steroid use, and presence of diabetes. OR for inflammation markers are presented for the effect of log-transformed interquartile range difference.

Concentrations of many inflammatory markers associated with atherosclerosis in the general population were higher in patients with SLE than in controls. Interestingly, the disease activity index (SLEDAI) correlated weakly with the ESR and CRP but not with other mediators. This may in part reflect the relatively low SLEDAI scores since the patient population had stable disease. However, it may also suggest that the SLEDAI does not identify important components of persistent inflammation as reflected by increased concentrations of adhesion molecules.

Adhesion molecules such as VCAM, ICAM, and E-selectin are detectable after injury to the endothelium, and may play a role early in the atherogenic process[32]. In animal models deletion of the genes coding for E-selectin or ICAM attenuated the development of atherosclerosis[33,34]. Also, in the general population, increased concentrations of adhesion molecules are associated with atherosclerosis[15,16]. However, in a single study, adhesion molecules (VCAM and ICAM) were not associated with the presence or absence of carotid plaque in SLE[4]. In our study, VCAM, ICAM, and E-selectin were associated with coronary calcification independent of Framingham risk score, diabetes, and cumulative corticosteroid dose. Interestingly, despite the association with coronary calcification, concentrations of VCAM in patients with

SLE were not significantly different from those of controls. This may imply that the role of VCAM in atherogenesis is enhanced in the setting of more active inflammation.

TNF-α is an important cytokine in inflammation and atherogenesis[35], and TNF-α concentrations are elevated in SLE[36]. There is little information about TNF-α and coronary calcium in any population[37], and our findings suggest that TNF-α may play a role in atherogenesis in SLE. The other potentially atherogenic inflammatory mediators (MPO, IL-1α, MMP-9, VEGF, CRP, SAA) were not significantly associated with coronary atherosclerosis after adjustment for Framingham risk score, diabetes, and corticosteroid exposure. Thus, it is likely that in the setting of persistent inflammation, specific mediators are associated with atherosclerosis.

We studied a population with asymptomatic, subclinical atherosclerosis. Thus, the findings suggest that adhesion molecules and TNF-α may contribute at a relatively early stage of atherosclerotic vascular disease in this population and therefore may represent a potential target for prevention of subsequent symptomatic atherosclerosis in patients with SLE.

Our study, which has the advantages of directly studying the relationship between inflammatory mediators and an objective measure of coronary atherosclerosis, has limitations. It was a cross-sectional study, and since atherogenesis is a longterm process, longitudinal studies including serial evaluations would provide additional valuable information. We did not adjust for multiple statistical comparisons since the hypotheses were prespecified; thus there is the possibility of detecting false-positive relationships due to multiple comparisons.

In conclusion, the adhesion molecules VCAM, ICAM, and E-selectin and cytokine TNF-α are associated with coronary atherosclerosis independent of Framingham risk score.

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