Coronary Calcium in Systemic Lupus Erythematosus Is Associated with Traditional Cardiovascular Risk Factors, But Not with Disease Activity

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ABSTRACT. ***Objective.*** Cardiovascular disease is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). The frequency of both subclinical and clinically evident atherosclerosis is greatly increased over healthy controls. We assessed cardiovascular risk factors present in patients with SLE at the baseline visit in a statin intervention trial and their correlation with coronary calcium.

Methods. Coronary calcium was measured by helical computed tomography (continuous volumetric data acquisition in a single breath-hold) in 200 patients with SLE enrolled in the Lupus Atherosclerosis Prevention Study.

Results. Patients had a mean age of 44.3 ± 11.4 years and were 92% women, 61% Caucasian, 34% African American, 2% Asian, and 2% Hispanic. Coronary calcium was found in 43%. In univariate analysis, coronary calcification was associated with age ($p = 0.0001$), hypertension ($p = 0.0008$), body mass index (BMI; $p = 0.03$), erythrocyte sedimentation rate (ESR; $p = 0.03$), anti-dsDNA ($p = 0.067$), and lipoprotein(a) ($p = 0.03$). Homocysteine ($p = 0.050$), high-sensitivity C-reactive protein (hsCRP; $p = 0.053$), and LDL ($p = 0.048$) had a stronger association when considered as quantitative predictors. In a multiple logistic regression model, only age ($p \leq 0.0001$) and body mass index ($p = 0.0014$) remained independent predictors. No measure of SLE activity was associated with coronary calcium. We also examined variables independently predictive of a coronary calcium score > 100. Based on a multiple logistic regression model, only age ($p = 0.0017$) and diabetes mellitus ($p = 0.019$) remained significant independent predictors of coronary calcium > 100.

Conclusion. Inflammation, measured as ESR or hsCRP, is associated with coronary calcium only in univariate analyses. Age, BMI, and diabetes mellitus are more important associates of coronary calcium in SLE than inflammatory markers and SLE clinical activity. (First Release May 15 2008; J Rheumatol 2008;35:1300–6)

Key Indexing Terms:
CORONARY CALCIUM
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Cardiovascular disease, specifically from atherosclerosis, is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE) in developed countries[1,2]. Atherosclerosis in SLE is multifactorial, with immune-mediated damage, traditional cardiovascular risk factors, and prothrombotic factors all playing important roles[3-5]. SLE patients aged 35 to 44 years were 50 times more likely to have a myocardial infarction than Framingham-study controls[6]. Traditional cardiovascular risk factors such as hypertension, hyperlipidemia, obesity, and smoking are common in SLE, and contribute to the cardiovascular risk[7]. However, traditional cardiovascular risk factors do not account for the entire risk[8].

Coronary calcium is closely associated with atherosclerotic plaque and serves as a surrogate measure of coronary atherosclerosis. A high correlation has been found between coronary calcification and total atherosclerotic burden, based on histopathological findings[9]. Coronary calcification scores are predictive of future cardiovascular events[10-14]. In the general population, age and sex are associated with coronary calcium scores[15].

Von Feldt, *et al* found that 38% of 13 patients with SLE had coronary calcification scores exceeding the 70th percentile of age-matched women[16]. In another study, 28% of 75 patients with SLE (ages 20–48 yrs, with no symptoms of coronary heart disease) had coronary artery calcification[17]. In a third study, coronary artery calcification was found in 30% of 65 SLE patients, with calcium scores ranging from

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0 to 1526 in patients versus 0 to 243.4 in 69 controls[18]. Coronary artery calcification was associated with inflammatory markers, including interleukin 6 and monocyte chemoattractant protein-1, in a study of 74 SLE patients and 85 controls[19].

We measured risk factors for atherosclerosis at the baseline visit of the Lupus Atherosclerosis Prevention Study, a 2-year intervention trial of atorvastatin versus placebo, and assessed their correlation with coronary calcium. All patients were part of the longitudinal Hopkins Lupus Cohort study, allowing quarterly assessment of cardiovascular risk factors, disease activity, and markers of inflammation in a prospective fashion from cohort entry. This is the largest study of coronary calcium in SLE, and the only study of coronary calcium with prospective assessment of disease activity, traditional cardiovascular risk factors, and measures of inflammation.

MATERIALS AND METHODS

Two hundred patients with SLE were enrolled in the Lupus Atherosclerosis Prevention Study. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All gave informed consent. Patients with a history of an atherosclerotic event (such as angina or myocardial infarction), LDL cholesterol level of 190 mg/dl, or triglyceride level > 500 mg/dl, for which statins are considered as part of standard clinical care, were excluded. However, 33.5% had a cholesterol measurement > 200 mg/dl, 8% had a cholesterol > 240 mg/dl, 47% had LDL > 100 mg/dl, 10% had elevated triglycerides, and 7% had low HDL.

As part of the Hopkins Lupus Cohort study, all patients had been seen quarterly since cohort entry, for assessment of disease activity by physician's global assessment [0 to 3 visual analog scale and the SELENA (Safety of Estrogens in Lupus Erythematosus: National Assessment) SLE Disease Activity Index (SLEDAI)[20,21]], laboratory tests [complete blood count, erythrocyte sedimentation rate (ESR), serum creatinine, cholesterol, urinalysis, C3, C4, and anti-dsDNA], and cardiovascular risk factors, including fasting lipid profile, homocysteine, lipoprotein(a) [Lp(a)], and fibrinogen. Hypertension was defined as persistent hypertension or hypertension under treatment. Insulin resistance was not measured.

Image acquisition and evaluation. Coronary calcification was assessed by helical computed tomography (CT) with a Siemens Volume Zoom Scanner (Siemens, Malvern, PA, USA) using a 2.5 mm collimation and a slice width of 3 mm. Data were reloaded into a Siemens Leonardo workstation, using the Siemens calcium scoring software. Coronary calcification was quantified using a standard scoring system, available as part of the scanner software package[22].

Statistical analysis. All results for continuous variables are expressed as means ± SD, unless specified otherwise. We used an "area under the curve" approach to calculate cumulative SELENA SLEDAI and cumulative prednisone measures from clinic information in the 2 years preceding the study.

To assess the association between predictors and the presence of coronary calcium, we divided the patients into groups based on the predictor variables, and compared the groups with respect to the proportion with coronary calcium. The statistical significance of observed differences was assessed using Pearson chi-square statistics, or Fisher's exact test, if needed due to small cell sizes. We also used logistic regression to assess the association between quantitative predictors and the presence of coronary calcium and to assess associations after adjusting for age. To assess the joint association between predictors and the presence of coronary calcium, we used forward stepwise logistic regression, retaining any term with a p value < 0.15.

RESULTS

Data were obtained on 200 subjects with SLE (92% women). The patients were 61% Caucasian, 34% African American, 2% Asian, 2% Hispanic, and 1% other ethnicity. Their mean age was 44.3 ± 11.4 years. Cumulative SLE clinical manifestations included malar rash 63%, discoid rash 23%, photosensitivity 60%, oral ulcers 54%, arthritis 80%, serositis 50%, renal disorder 40%, neurological disorder 9%, immunologic disorder 75%, and antinuclear anti-

Table 1. Presence of coronary calcium, by demographic, lipid, and nonlipid traditional risk factors (univariate analysis).

	Proportion with any Coronary Calcium (%)	p	Proportion with Coronary Calcium > 100 (%)	p
Age group, yrs				
18–39	15/62 (24)	0.0001	2/62 (3)	0.033
40–49	31/73 (43)		6/73 (8)	
50–59	28/50 (56)		5/50 (10)	
60+	11/15 (73)		4/15 (27)	
Female	78/184 (42)	0.92	16/184 (9)	1.0
Male	7/16 (44)		1/16 (6)	
Ethnicity				
African American	32/66 (48)	0.27	5/66 (8)	0.94
Caucasian	50/122 (41)		11/122 (9)	
Other	3/12 (25)		1/12 (9)	
Lipid and nonlipid traditional risk factors				
Body mass index				
< 25	22/66 (33)	0.0301	5/66 (8)	0.38
25–30	27/69 (39)		4/69 (6)	
30+	36/65 (55)		8/65 (12)	
Hypertension				
No	32/103 (31)	0.0008	5/103 (3)	0.057
Yes	53/97 (55)		12/97 (12)	
Mean systolic blood pressure in preceding 2 yrs, mm Hg				
< 120	34/104 (33)	0.013	6/104 (6)	0.0067
120–130	26/51 (51)		2/51 (4)	
130+	25/45 (56)		9/45 (20)	
Smoking				
No	68/166 (41)	0.27	12/166 (7)	0.11
Yes	16/31 (52)		5/31 (16)	
Diabetes mellitus				
No	78/189 (41)	0.14	14/189 (7)	0.055
Yes	7/11 (64)		3/11 (27)	
Total cholesterol, mg/dl				
≤ 200	51/133 (38)	0.094	9/133 (7)	0.21
201+	34/67 (51)		8/67 (12)	
LDL cholesterol, mg/dl				
< 100	38/102 (37)	0.24	4/102 (4)	0.054
100–129	26/52 (50)		7/52 (13)	
130+	21/44 (48)		6/44 (14)	
HDL cholesterol, mg/dl				
< 40	8/20 (40)	0.96	2/20 (10)	0.69
40–59	39/90 (43)		6/90 (7)	
60+	38/89 (43)		9/89 (10)	
Triglycerides, mg/dl				
< 150	70/161 (43)	0.65	13/161 (8)	0.75
150+	15/38 (39)		4/38 (11)	

body positivity 97%. Coronary calcium was found in 43%, with scores ranging from 0.1 to 3885.3. A coronary calcium score > 100 was found in 9%. The associations between coronary calcium and patient characteristics are summarized in Tables 1, 2, and 3.

Coronary calcium was significantly associated with age (p = 0.0001), hypertension (p = 0.0008) and body mass index (BMI) (p = 0.03) (Table 1). Fibrinogen (378.3 vs 350.6), homocysteine (12.3 vs 11.7), and Lp(a) (66.2 vs 63.6) were all higher in those with coronary calcium, with Lp(a) being statistically significant (Table 2). Even in patients without coronary calcification, high-sensitivity C-reactive protein (hsCRP) was in the high-risk range for the general population, with a mean of 7.7 mg/l in those with coronary calcium and 4.2 mg/l in those without coronary calcium. The ESR was also associated with coronary calcium (p = 0.03). Among serologic markers, only anti-dsDNA had a borderline association with coronary calcium (p = 0.067; Table 3). The cumulative disease activity in the 2 years before the helical CT was not associated with coronary calcium. Coronary calcium was more likely to be present in those who had ever used prednisone (46%) than in those who had not (29%) (p = 0.06; Table 3).

We also looked at the relationship between quantitative characteristics and the probability of having coronary calcium using logistic regression, treating the characteristic as continuous. In general, the p values for the variables were similar to those seen in Tables 1 to 3. There was a stronger association between coronary calcium and homocysteine (p = 0.050), hsCRP (p = 0.053), and LDL cholesterol (p = 0.048) when these were considered as quantitative predictors.

Because age is likely to be a strong confounder of many of the relationships shown in Tables 1–3, we performed an additional analysis, assessing the associations in Tables 1–3 after adjusting for age. After adjusting for age, all of the associations in Tables 1–3 with respect to the presence of any coronary calcium remained qualitatively the same, with the following exceptions: the association with mean systolic blood pressure in the preceding 2 years was no longer statistically significant (p = 0.19), the association with Lp(a) was no longer significant (p = 0.70), the association with fibrinogen became statistically significant (p = 0.0091), the p value for the association with total cholesterol increased, and that for anti-dsDNA had a sizeable increase (to p = 0.56 and p = 0.32, respectively).

In the multiple logistic regression model, age (p ≤ 0.0001) and BMI (p = 0.0014) remained statistically significant independent predictors, while prednisone exposure, hypertension, and fibrinogen were marginally associated with coronary calcium after controlling for the other variables in the model (Table 4).

We also did a univariate analysis for variables predictive of coronary calcium in patients with a coronary calcium score > 100. Besides age (p = 0.033), mean systolic blood pressure (in the 2 years preceding the helical CT scan; p = 0.0067), diabetes mellitus (p = 0.055), and LDL cholesterol were associated (p = 0.054) with coronary calcium > 100. However, only 17 patients had a coronary calcium score > 100. Based on a multiple logistic regression model, only age (p = 0.0017) and diabetes mellitus (p = 0.019) remained significant independent predictors of a coronary calcium score > 100 (Table 5).

DISCUSSION

This study, the largest study of coronary calcium in SLE, confirms the importance of traditional cardiovascular risk factors, including age, hypertension, diabetes mellitus, and obesity, in the accelerated atherosclerosis of lupus. Hypertension, diabetes mellitus, and obesity are modifiable risk factors, increasing their relevance in clinical practice.

We addressed whether control of hypertension was important. The mean systolic blood pressure in the 2 years before the helical CT examination was significantly associated with coronary calcium. A much higher proportion of patients (20%) with a systolic blood pressure > 130 mm Hg had coronary calcium versus those below 130 mm Hg (5%). Our data indicate that stringent control of hypertension in SLE should be the goal. In the general population, nearly three-fourths of US adults with cardiovascular morbidity have poor control rates of systolic hypertension[23].

Table 2. Presence of coronary calcium, by novel markers of atherosclerosis (univariate analysis).

Marker	Proportion with any Coronary Calcium (%)	p	Proportion with Coronary Calcium > 100 (%)	p
Homocysteine, mg/dl				
< 10	24/62 (39)	0.47	4/62 (6)	0.49
10+	61/138 (44)		13/138 (9)	
Fibrinogen, mg/dl				
≤ 400	56/145 (39)	0.072	12/145 (8)	0.85
401+	29/55 (53)		5/55 (9)	
Lipoprotein (a), mg/dl				
< 30	29/86 (34)	0.029	10/86 (12)	0.17
30+	56/114 (49)		7/114 (6)	

Table 3. Presence of coronary calcium, by SLE variables, treatment, and inflammatory markers (univariate analysis).

	Proportion with any Coronary Calcium (%)	p	Proportion with Coronary Calcium > 100 (%)	p
SLE variables				
C3				
Normal or high	72/170 (42)	0.57	13/170 (8)	0.26
Low	13/27 (48)		4/27 (15)	
C4				
Normal or high	77/171 (45)	0.16	16/171 (9)	0.71
Low	8/26 (31)		1/26 (4)	
Presence of anti-dsDNA				
No	70/150 (47)	0.06	14/150 (10)	0.37
Yes	14/46 (30)		2/46 (4)	
SELENA SLEDAI				
< 4	64/154 (42)	0.47	11/154 (7)	0.18
4+	21/44 (48)		6/44 (14)	
Cumulative SELENA SLEDAI in preceding 2 yrs				
0	12/23 (52)	0.23	3/23 (13)	0.18
> 0 but < 1 per day	23/63 (37)		7/63 (11)	
> 1 per day	24/46 (52)		1/46 (2)	
> 2 per day	25/67 (37)		6/67 (9)	
Duration of SLE (since diagnosis), yrs				
< 5	24/61 (39)	0.70	7/61 (11)	0.33
5–10	22/52 (42)		2/52 (4)	
> 10	38/82 (46)		8/82 (106)	
Treatment				
Prednisone use ever				
No	11/38 (29)	0.060	2/38 (5)	0.75
Yes	74/162 (46)		15/162 (9)	
Cumulative prednisone in preceding 2 yrs				
None	37/94 (39)	0.65	7/94 (7)	0.74
Average < 5 mg/day	29/62 (47)		5/62 (8)	
Average ≥ 5 mg/day	19/44 (43)		5/44 (11)	
Prednisone (at time of coronary calcium study)				
None	48/114 (42)	0.53	11/114 (10)	0.52
< 10 mg/day	23/59 (40)		3/59 (5)	
10+ mg/day	14/27 (52)		3/27 (11)	
Hormone therapy				
No	61/149 (41)	0.32	12/149 (8)	0.52
Yes	18/36 (50)		4/36 (11)	
Inflammatory markers				
hsCRP, mg/l				
≤ 3	40/106 (38)	0.15	6/106 (6)	0.13
> 3	45/94 (48)		11/94 (12)	
ESR				
Low	18/59 (31)	0.030	4/59 (7)	0.78
High (> 25 mm/h)	66/140 (47)		13/140 (9)	

SELENA: Safety of Estrogens in Lupus Erythematosus: National Assessment. SLEDAI: SLE Disease Activity Index. hsCRP: high-sensitivity C-reactive protein, ESR: erythrocyte sedimentation rate.

High BMI was strongly associated with adverse cardiovascular factors including CRP, fibrinogen, and intracellular adhesion molecule-1 in the Women's Health Study[24]. We confirm the importance of obesity as a risk factor for coronary calcium in SLE. Obesity and inflammatory markers were correlated in a cross-sectional analysis of 27,158 healthy women in the Women's Health Study[24]. In our study, ESR and hsCRP were associated with coronary calcium in univariate analysis. However, neither hsCRP nor ESR was associated with coronary calcium in our multivariate models after adjusting for age and BMI.

In strong contradistinction to the general population, lipids have been found not to be a major cardiovascular risk factor in patients with SLE[25]. In our study, no lipid marker was associated with coronary calcium in multivariate models. Proinflammatory HDL has recently been reported to be

Table 4. Variables independently predictive of coronary calcium, based on a multiple logistic regression model.

Variable	Comparison	OR (95% CI)	p
Age	Per 10 years of life	2.1 (1.5, 2.9)	< 0.0001
Body mass index	Per 5 unit change	1.4 (1.1, 2.0)	0.0014
Hypertension	Present vs absent	1.7 (0.9, 3.4)	0.13
Fibrinogen	Per 1 SD increase	3.1 (0.8, 12.4)	0.11
Cumulative prednisone	Per 10 mg/day, 1 yr	1.4 (1.0, 2.0)	0.073

Table 5. Variables independently predictive of coronary calcium score > 100, based on a multiple logistic regression model.

Variable	Comparison	OR (95% CI)	p
Age	Per 10 years of life	2.6 (1.4, 4.6)	0.0017
SLEDAI ≥ 4	vs lower	3.0 (0.8, 11.9)	0.11
Smoking	Yes vs no	3.8 (1.0, 14.6)	0.055
Diabetes mellitus	Yes vs no	8.9 (1.4, 55.6)	0.019
LDL cholesterol	Per 1 SD increase	6.0 (0.8, 47.9)	0.091

associated with cardiovascular disease in SLE, and may represent the "missing link" between lipids and atherosclerosis in SLE[26].

In terms of novel risk factors, homocysteine and Lp(a) were associated with coronary calcium in univariate models. Homocysteine is also a risk factor for stroke in SLE[27]. Multiple groups have shown that elevated levels of homocysteine are frequent in SLE[28,29]. However, the utility of interventions to lower homocysteine has been questioned, because multiple clinical trials in the general population have been negative[30,31]. However, a metaanalysis of randomized trials to assess the efficacy of folic acid supplementation for hyperhomocysteinemia did show a significant reduction in the risk of stroke[32].

Lp(a) is also a risk factor for stroke in some[33] but not all studies[34] in the general population. Elevated levels of Lp(a) are frequent in autoimmune diseases, including rheumatoid arthritis and SLE[35-37]. Several drugs, including aspirin and statins, have been shown to reduce Lp(a) levels[38,39], although the utility of interventions to lower Lp(a) has been in question[40].

Although atherosclerosis has been found to have an earlier onset in patients with SLE than in the general population, age remained a risk factor for coronary calcium in SLE in our study and others[41,42]. Ours is the first study to include a large number of African American patients with SLE. However, there was no significant difference in the frequency of coronary calcium in African Americans (49%) compared to Caucasians (41%) with SLE. This is not the case in the general population, in which coronary calcium is more prevalent in Caucasians[43].

The role SLE itself plays in the pathogenesis of accelerated atherosclerosis was extensively evaluated in our study. Both hsCRP and the ESR were associated with coronary calcium in univariate analyses. Indeed, the level of hsCRP in those SLE patients without coronary calcium would still have been considered "high risk" in the general population. However, a hsCRP > 3 failed to reach statistical significance in the multivariate analysis of coronary calcium[44]. Disease activity, measured as the physician's global assessment, the SELENA SLEDAI, anti-dsDNA, or low complement, was not associated with coronary calcium in multivariate analysis. Even the cumulative disease activity and prednisone in the 2 years prior to the helical CT scan were not associated with coronary calcium. This is in agreement with our previous studies on carotid atherosclerosis, as well[45].

We have previously shown that the sickest patients with SLE (those that require high-dose corticosteroids or pulse intravenous methylprednisolone) are not the group at greatest risk for coronary artery disease[46]. Instead, it appears that SLE patients taking longterm prednisone, even low doses, are at risk for coronary artery disease. We have also shown that prednisone use increases traditional cardiovascular risk factors, including hypertension, cholesterol, and weight[6]. In this study, prednisone use was more frequent in those with coronary calcium (46% vs 29% in those without). We cannot discriminate, however, between prednisone use itself, and the reason prednisone was given, namely, ongoing SLE activity. Hormone therapy, known to increase coronary artery disease in the general population[47], was not associated with coronary calcium in patients with SLE.

Our study cannot address whether coronary calcium is predictive of angina or myocardial infarction in SLE, although this has been proven in the general population[11,48,49]. Women at low risk for cardiovascular disease (based on the Framingham score) who had a coronary calcium score greater than zero were found to be at increased risk for heart disease in the MESA study[49]. Coronary calcium has been recommended as the preferred measure of subclinical atherosclerosis in the general population[50].

Our results indicate that certain cardiovascular risk factors (hypertension, diabetes mellitus, and obesity) should be targeted for intervention in patients with SLE. Measures of inflammation such as hsCRP and a high ESR were associated with coronary calcium only in univariate, not multivariate, models. Even for the highest level of coronary calcium, traditional cardiovascular risk factors are more important associates of coronary calcium than any SLE-associated factors.

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