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Original article

Coronary calcification in SLE: comparison with the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective. Accelerated atherosclerosis is a major cause of morbidity and death in SLE. The purpose of this study was to determine whether the prevalence and extent of coronary artery calcium (CAC) is higher in female SLE patients compared with a non-SLE sample from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods. CAC was measured in 80 female SLE patients and 241 female MESA controls from the Baltimore Field Centre, ages 45–64 years, without evidence of clinical cardiovascular disease. Binary regression was used to estimate the ratio of CAC prevalence in SLE *vs* MESA controls, controlling for demographic and cardiovascular risk factors. To compare the groups with respect to the quantity of CAC among those with non-zero Agatston scores, we used linear models in which the outcome was a log-transformed Agatston score.

Results. The prevalence of CAC was substantially higher in SLE. The differences were most pronounced and statistically significant in those aged 45–54 years (58% *vs* 20%, $P < 0.0001$), but were still observed among those aged 55–65 years (57% *vs* 36%, $P = 0.069$). After controlling for age, ethnicity, education, income, diabetes mellitus, hypertension, hyperlipidaemia, high-density lipoprotein levels, smoking, education and BMI, SLE patients still had a significantly higher prevalence of CAC than controls. Among those with CAC, the mean log Agatston score did not differ significantly between SLE and MESA participants.

Conclusion. Women with SLE have a higher prevalence of CAC than comparable women without SLE, even after adjusting for traditional cardiovascular risk factors, especially among those aged 45–54 years.

Key words: systemic lupus erythematosus, atherosclerosis, coronary artery calcium, inflammation, MESA, computed tomography, statins, cardiovascular, Agatston score, cohort.

CLINICAL SCIENCE

Rheumatology key messages

- Women with SLE have a higher prevalence of coronary artery calcification than comparable women without SLE.
- The aetiology of the increased prevalence of coronary artery calcification in SLE is multifactorial.

Introduction

Cardiovascular disease burden is increased in patients with SLE [1, 2]. We have recently shown a 2.7-fold increased risk of acute cardiovascular events in SLE patients relative to that expected based on a Framingham risk score [3], thus confirming previous reports of excess cardiovascular disease among patients with SLE [4–7]. Multiple factors play a role in the increased incidence of cardiovascular events in SLE [8–11].

In the general population, coronary artery calcium (CAC) scores are predictive of atherosclerotic burden [12] and

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future cardiovascular events [13–16]. Even after controlling for the Framingham Risk Score, CAC is significantly associated with incident events [17]. Absolute scores are better predictors than percentiles of CAC based on age and gender among participants in the Multi-Ethnic Study of Atherosclerosis (MESA) [18]. An analysis of four racial and ethnic groups in MESA showed that doubling the CAC score increased the risk of a major coronary event by 15–35% [19]. Histological studies have also confirmed the correlation between the extent of calcified plaque and overall plaque burden [20, 21].

We hypothesized that the extent of CAC would be higher in women with SLE than in comparable women without SLE. To address this hypothesis, we compared a subset of women in the Hopkins Lupus Cohort with a subset of non-SLE patients from the MESA with respect to the prevalence and quantity of CAC and traditional cardiovascular risk factors.

Materials and methods

Lupus Atherosclerosis Prevention Study

SLE patients included in the Lupus Atherosclerosis Prevention Study (LAPS) were drawn from participants in the Hopkins Lupus Cohort who consented to participate in a 2 year randomized double-blind placebo-controlled trial of atorvastatin 40 mg *vs* matching placebo [22]. Patients with a history of angina or myocardial infarction, triglyceride level of >500 mg/dl or low-density lipoprotein cholesterol (LDL-C) level of >190 mg/dl were excluded. Patients were also excluded if they were taking lipid-lowering medication. CAC scores were measured by multidetector CT at baseline and 2 years later. MESA was approved by the Johns Hopkins Institutional Review Board. This trial, which included 200 participants, was completed and did not show any benefit of atorvastatin in the reduction of atherosclerosis progression in SLE. Because the SLE clinical trial excluded patients who had a history of cardiovascular disease, high triglycerides or high LDL, they tended to have fewer cardiovascular risk factors than the general cohort. Specifically, whereas only 5/80 (6%) of the SLE clinical trial patients had a history of diabetes, 14% of comparable members of the general cohort had a history of diabetes. Also, SLE patients in the clinical trial were somewhat less likely to have a BMI >30 (35% *vs* 39%). However, roughly equal proportions had a history of smoking (47% in the SLE clinical trial *vs* 43%) and SLE patients in the clinical trial were more likely to have hypertension (76% *vs* 67%).

All female LAPS participants who were between 45 and 64 years of age were included in this analysis ($n = 80$). We excluded males ($n = 9$) and those >65 years of age ($n = 10$) because their numbers were very small, and we excluded those <45 years of age because the MESA comparison group only included participants ⩾45 years of age. Our analysis was based on the baseline CT assessments completed between May 2002 and November 2004.

MESA control subjects

Comparison patients in this study were drawn from the Baltimore subset of the MESA cohort. MESA is a multicentre observational cohort study designed to investigate the prevalence, incidence and risk factors associated with the development and progression of subclinical and clinical cardiovascular disease. The MESA cohort (6814) includes participants aged 45–84 years from four racial/ethnic groups from six US communities, with Baltimore being one of the sites [23]. MESA participants were free of known cardiovascular disease at baseline [23]. Characteristics of MESA participants and the MESA design and methods have been described elsewhere [23]. The Johns Hopkins University School of Medicine Institutional Review Board (IRB) approved the MESA/Baltimore study.

Participants in the MESA were included in this analysis if they were female, 45–64 years of age and recruited from the Baltimore Field Centre. To be comparable to the SLE patients, we excluded those with a fasting triglyceride level >500 mg/dl, an LDL-C level >190 mg/dl and those on lipid-reducing medication. Our analysis was based on all 241 MESA participants who satisfied these criteria. Our analysis was based on the baseline MESA assessment conducted in 2000–2002. Our study was approved by the Johns Hopkins IRB (NA_00072872, Subclinical Atherosclerosis in Lupus Patients and MESA Controls in Baltimore).

Measurement of cardiovascular risk factors

In the SLE patients, diabetes mellitus was defined as diabetes requiring an oral hypoglycaemic agent or insulin, whereas in MESA it was defined as a positive response to the question regarding taking medications for diabetes or a fasting glucose of 126 mg/dl. Hypertension in both groups was defined as a systolic blood pressure ⩾140 mmHg or a diastolic blood pressure ⩾90 mmHg or use of antihypertensive medication at the time of the CAC examination. Other risk factors were defined based on clinical measurements taken at the time of the CAC examination or by interviewers at the time of enrolment. The fasting lipid profile [including total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides] was performed on the c8000 Chemistry Analyzer using reagents for total cholesterol, LDL-C, HDL-C and triglycerides (Roche Diagnostics, Indianapolis, IN, USA). LDL was calculated, whereas the rest were measured. BMI was calculated using the formula weight in kilograms divided by height in metres.

Measurement of coronary artery calcification

Coronary artery calcification was assessed by multidetector CT with a Siemens Volume Zoom Scanner (Siemens Medical Solutions, Malvern, PA, USA) using a 2.5-mm collimation and a slice width of 3 mm for the SLE patients. Data were reloaded into a Siemens Leonardo workstation using the Siemens calcium scoring software. Coronary artery calcification was quantified using a standard scoring system, available as part of the scanner software

package [24], and scores were calculated using the Agatston method [25]. In the absence of calcification, the score takes the value of zero. Minimal levels of identifiable calcification are scored between 1 and 10, mild between 11 and 100, moderate between 101 and 400 and extensive ⩾401. MESA participants underwent multidetector CT scanning and CAC scores were quantified, as described elsewhere [25, 26]. Chest CT was performed using an electrocardiogram-triggered scan acquisition at 50% of the R–R interval with a multidetector CT system acquiring a block of four 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode.

To address the possibility of a systematic difference between MESA and SLE clinical trial assessments of coronary calcium, we performed a study of agreement in 18 participants. Categorized as 0, 1–10, 11–100, 101–400 and ⩾401, the two assessments resulted in the same category in 15/18 cases, and the 3 cases that were discordant were only off by one category.

Statistical methods

To assess the statistical significance of differences between MESA and SLE participants with respect to the proportion with CAC within broad age groups, we used the chi-square test. To compare the groups with respect to the prevalence of CAC after adjusting for differences in age and other cardiovascular risk factors, we used prevalence ratio multiple regression models based on the method described by Zou [27]. To compare the groups with respect to the quantity of CAC among those with non-zero Agatston scores while adjusting for age, race and other potential confounders, we used linear regression models. Due to the fact that the Agatston scores were right skewed, we based these models on the log Agatston scores.

Results

Eighty SLE patients and 241 MESA controls were included in this study. Demographic characteristics of the two groups are shown in Table 1. A higher proportion of the SLE patients than controls was <55 years of age (71% *vs* 52%) and Caucasian (65% *vs* 41%). The MESA controls were somewhat more likely to have had some college education (77% *vs* 61%) (Table 1).

Table 2 shows the differences between SLE patients and MESA controls, by age group, with respect to various cardiovascular risk factors. In the older age group, SLE patients were less likely to have diabetes (4% *vs* 14%), a history of smoking (35% *vs* 52%) and low HDL-C (18% *vs* 36%). In the younger age group (45–54), SLE patients were somewhat more likely to have hypertension (51% *vs* 32%), but less likely to have a BMI >30 (33% *vs* 52%) (Table 2).

Table 3 shows the difference in the prevalence of CAC between the two groups, by age. In both age groups, SLE patients had a substantially higher prevalence of CAC than the MESA controls, but the disparity was greatest in the younger group ($P = 0.0026$ for interaction between continuous age and SLE status). These relationships persisted after adjusting for other risk factors in a multivariable model (Table 3). Because the unadjusted analysis suggested that the prevalence ratio due to SLE was heterogeneous with regard to age, we included a term to allow the log-prevalence ratio to change linearly with age. For example, for those 50 years of age, the estimated prevalence ratio was 2.8 (95% CI 1.9, 4.2; $P < 0.0001$), while for those 60 years of age, the prevalence ratio was 1.5 (95% CI 0.9, 2.3; $P = 0.13$) ($P = 0.017$ for the interaction).

This association persisted if we defined CAC as an Agatston score >10. Specifically, in the younger age group, using 10 as a cut-off, there was still a significantly higher prevalence of CAC among the SLE patients (32% *vs* 14%, $P = 0.007$). However, using this cut-off in the older age group, there was surprisingly a lower prevalence of CAC in the small sample of SLE patients in this age group [5/23 (22%)] *vs* the MESA patients [36/116 (31%)], although this difference was not statistically significant ($P = 0.37$).

Table 4 shows the mean log Agatston score by group and age among those with non-zero Agatston scores. Among those with CAC present, there were no significant differences in the quantity of CAC between the two groups, although surprisingly the mean score was lower among those in the SLE clinical trial patients. Adjusting for other cardiovascular risk factors did not result in a significant difference between the groups with respect to the mean log Agatston score. There was no significant interaction between age groups and age with respect to mean log Agatston score.

The lower mean scores among those in the SLE clinical trial were attributed to a higher rate of low-level calcium

Table 1 Demographic characteristics of SLE patients and a subset of the MESA participants

	SLE patients ($n = 80$), *n* (%)	MESA controls ($n = 241$), *n* (%)
Age group, years		
45–54	57 (71)	125 (52)
55–64	23 (29)	116 (48)
Ethnicity		
Caucasian	52 (65)	98 (41)
African American	25 (31)	143 (59)
Other	3 (3)	0 (0)
Years of education		
<High school	6 (8)	18 (8)
High school	25 (31)	37 (16)
Some college	19 (24)	92 (39)
College graduate	30 (38)	91 (38)
Annual family income		
<$35 000	27 (34)	75 (31)
$35 000–74 999	29 (36)	96 (40)
⩾$75 000	21 (26)	61 (25)
Unknown	3 (4)	9 (4)

MESA: Multi-Ethnic Study of Atherosclerosis.

Table 2 Cardiovascular risk factors in SLE patients and a subset of the MESA participants by age group

Risk factor	Age 45–54 years		Age 55–64 years	
	SLE patients ($n = 57$), n (%)	MESA controls ($n = 125$), n (%)	SLE patients ($n = 23$), n (%)	MESA controls ($n = 116$), n (%)
Diabetes mellitus	3 (5)	0 (0)	1 (4)	14 (14)
History of smoking	26 (46)	60 (49)	8 (35)	60 (52)
Hypertension	29 (51)	41 (33)	14 (61)	66 (57)
Total cholesterol >200 mg/dl	28 (49)	52 (43)	11 (48)	56 (49)
LDL-C >130 mg/dl	17 (30)	34 (28)	7 (32)	40 (35)
HDL-C <50 mg/dl	12 (21)	41 (34)	4 (18)	41 (36)
BMI >30 kg/m^2	19 (33)	65 (52)	9 (39)	55 (47)

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MESA: Multi-Ethnic Study of Atherosclerosis.

Table 3 Prevalence of coronary calcium in SLE patients and a subset of MESA participants by age group

Age group, years	SLE patients with coronary calcium, n/N (%)	MESA participants with coronary calcium, n/N (%)	P-value[a]	Adjusted prevalence ratio[b] (95% CI)	Adjusted P-value[b]
45–54	33/57 (58)	25/125 (20)	<0.0001	2.8 (1.9, 4.0)	<0.0001
55–64	13/23 (57)	42/116 (36)	0.069	1.4 (0.9, 2.3)	0.14

[a]Based on a chi-square test. [b]Based on a binary regression model adjusting for age (continuous), ethnicity, education, income, diabetes, hypertension, low HDL-C, high LDL-C, smoking and BMI. The adjusted prevalence ratio in the first row refers to individuals who were 50 years of age, while the prevalence ratio in the second row refers to those who were 60 years of age. The interaction between age and SLE was found to be statistically significant ($P = 0.017$). HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MESA: Multi-Ethnic Study of Atherosclerosis.

Table 4 Mean log Agatston score of SLE patients and a subset of the MESA participants by age group (among those with CAC)

Age group, years	SLE		MESA		P-value[a]	Adjusted mean difference[b]	Adjusted P-value[b]
	n	Mean (S.D.)	n	Mean (S.D.)			
45–54	33	2.6 (2.2)	25	3.0 (1.2)	0.50	−0.55	0.34
55–64	13	2.2 (2.4)	42	4.1 (1.7)	0.12	−0.48	0.61

[a]Adjusted for age within age groups. [b]Based on a regression model adjusting for age (continuous), ethnicity, education, income, diabetes, hypertension, low HDL-C, high LDL-C, smoking and BMI. CAC: coronary artery calcium; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MESA: Multi-Ethnic Study of Atherosclerosis.

scores. Among those with CAC in the SLE clinical trial, 50% had a score between 1 and 10 compared with only 20% among those in the MESA.

Discussion

We found a strikingly higher prevalence of CAC in female SLE patients compared with MESA controls, which was significant for women aged 45–55 years ($P < 0.0001$). After adjustment for ethnicity, hypertension, lipids, diabetes mellitus, smoking and BMI, the prevalence ratio was approximately the same as that for the unadjusted estimate. This suggests that, in our study, the observed increase in CAC among SLE patients could not be explained by traditional cardiovascular risk factors alone. Thus risk assessment of SLE patients by considering only traditional risk factors would underestimate their cardiovascular risk.

Our observations are consistent with results found in several previous studies that compared SLE patients with controls with respect to CAC [28–31]. However, our

study includes a much larger number of population-based controls than previous studies, including African Americans. In past studies, controls were recruited from clinics. In addition, we adjusted not only for traditional cardiovascular risk factors, but also for education and ethnicity. We therefore believe our study provides a better picture of increased prevalence of CAC among SLE patients compared with controls.

The higher prevalence ratio of CAC in younger women is consistent with previous observations that the excess cardiovascular event rates among SLE patients are most pronounced in younger groups. Another possible explanation could be due to selection bias, as older patients with SLE are survivors and those with CAC may have died before reaching older age. In a recent publication we estimated a 5-fold increase in the cardiovascular event rate among men and women $<$40 years of age, while the excess (relative) risk in age groups $>$40 years ranged from 1.9 to 2.69 [3]. Earlier, Manzi *et al*. [6] observed a 50-fold increase in the myocardial infarction rate among SLE female patients aged 35–44 years [6]. A larger disparity in CAC prevalence among younger ages was also observed in a previous comparison between MESA participants and patients with RA [32].

Systemic inflammatory processes influence plaque formation and calcification by favouring oxidative damage, leading to increased pro-inflammatory cytokines [33]. This possible mechanism may explain the disparity between SLE and control individuals, even after adjusting for ethnicity and cardiovascular risk factors.

To gain insight into the aetiology of the excess atherosclerosis among patients with SLE, we previously compared SLE patients with CAC with those without CAC with respect to SLE-related risk factors. In that analysis we did not observe strong evidence of an association between CAC and various SLE-related risk factors (including disease duration, disease activity, low complement, anti-dsDNA and corticosteroid use) [34].

Several other research teams have performed similar analyses with conflicting results. Von Feldt *et al*. [28] observed a statistically significant association between SLE disease duration and CAC after adjustment for age, and Romero-Díaz *et al.* [31] observed an association between several measures of disease severity and CAC.

One of the limitations of this study is that the SLE patients were scanned on a different machine from the MESA controls, which could lead to systematic differences in the CAC scores. It is also possible that there might be some residual confounding since this was an observational study. An additional limitation is that our study was cross-sectional and thus selection and temporal biases may have occurred.

Because male patients, Asians and Hispanics were not included as part of the current cohort, this limits the external validity of our current results. We did not include patients with very high levels of cholesterol or triglycerides because we felt it would be unethical to prevent these patients from using statins as part of routine standard of care.

In summary, we observed a greater prevalence of CAC in SLE patients than in MESA controls, even after adjusting for key confounders. We also found a higher prevalence ratio of CAC in younger SLE patients. However, among those with CAC in both populations, there were no significant differences in Agatston score between SLE and MESA samples. The aetiology of the increased prevalence of coronary artery calcification in SLE is almost certainly multifactorial. Until the SLE-specific risk factors can be identified and measured, targeting traditional cardiovascular risk factors in SLE patients remains a priority. One of the limitations of this study is that the SLE patients were scanned on a different machine from the MESA controls, which could lead to systematic differences in the CAC scores [35].

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