

Asymptomatic Coronary Artery Calcifications in Men with Systemic Lupus Erythematosus

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ABSTRACT. Objective. To determine whether the prevalence and extent of asymptomatic coronary artery atherosclerosis are increased in men with systemic lupus erythematosus (SLE) compared with age- and sex-matched controls, and to define the associated risk factors.

Methods. Ninety-five patients with SLE (mean \pm SD age, 34.7 \pm 10.1 yrs) and 100 control subjects (age 34.8 \pm 9.7 yrs) with no history of coronary artery disease were screened for coronary artery calcification using multidetector computed tomography. The extent of calcification was measured using the Agatston score. The frequency of risk factors for calcification was compared between patients and controls, and the relationship between clinical and immunological characteristics and the presence of coronary artery calcification was investigated.

Results. Coronary artery calcification was more frequent in patients than controls [18% vs 7%, respectively (OR 2.89, 95% CI 1.07–8.65)]. These factors were independently associated with the presence of calcifications: age (OR 1.12, 95% CI 1.04–1.20), SLE diagnosis (OR 3.38, 95% CI 1.07–10.64), diabetes mellitus (OR 6.88, 95% CI 1.50–31.62), Framingham risk score (OR 1.12, 95% CI 1.00–1.23), and glomerular filtration rate (OR 0.98, 95% CI 0.96–1.00). Among patients with SLE, coronary artery calcifications were observed starting at age 32 years, within 2.3 years of diagnosis. Increasing age (OR 1.18, 95% CI 1.06–1.31), Systemic Lupus International Collaborating Clinics score (OR 2.85, 95% CI 1.21–6.73), and cumulative dose of prednisone (OR 1.04, 95% CI 1.01–1.08) were independent risk factors.

Conclusion. Men with SLE are at an increased risk of coronary artery calcifications than age- and sex-matched controls. Among patients with SLE, the increased risk is associated to older age, increasing chronic damage, and cumulative dose of corticosteroids. (J Rheumatol First Release March 15 2018; doi:10.3899/jrheum.170330)

Key Indexing Terms:

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Systemic lupus erythematosus (SLE) is an autoimmune disease that mainly affects young women. The estimated prevalence is 72.8–74.4 per 100,000 persons, but it varies according to age, sex, and race^{1,2}. The Lupus Foundation of America estimates that 1.5 million Americans, and at least 5

million people worldwide, have a form of SLE; systemic lupus accounts for about 70% of all cases, and 10% of individuals diagnosed with the disease are men (www.lupus.org).

The survival rate of patients with SLE has improved significantly owing to a decline in all-cause mortality;

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however, the risk of death due to circulatory diseases remains unchanged and they are now among the leading causes³.

Premature atherosclerosis occurs more often in SLE than in the general population. The rate of myocardial infarction in young women may be up to 50-fold higher than in age-matched controls⁴; and subclinical atherosclerosis is detected in 30–43% of patients versus 9–16% of controls^{5,6,7,8}. The increased risk is attributed not just to the presence of traditional cardiovascular (CV) risk factors, but to the underlying inflammatory disease and/or its treatment⁹.

Existing knowledge about the burden and risk factors of atherosclerosis in SLE derives from studies in which 85–100% of participants were women^{4,5,6,7,8,9}; however, atherosclerosis affects men and women differently regarding incidence, prevalence, risk factors, pathogenesis, clinical manifestations, treatment, morbidity, and mortality^{10,11,12}. For optimal prevention and treatment of atherosclerosis, it is not self-evident that women and men show similar responses to risk factors or to treatment; therefore, it is essential that studies present results according to sex. Whether the threat and risk factors of premature atherosclerosis in women with SLE are generalized to male patients is unknown.

Coronary artery atherosclerosis can be detected noninvasively with the use of electron-beam computed tomography. The extent of coronary artery calcification correlates with findings on coronary angiography, with the extent of atherosclerosis in pathological specimens, and is predictive of future cardiac events^{13,14,15,16,17,18,19}. Coronary artery calcium scanning has emerged as one of the strongest predictors of coronary events in the asymptomatic population, particularly in the intermediate-risk cohort²⁰. It is also strongly associated with the development of stroke and congestive heart failure²¹.

Because of the scarcity of data about premature atherosclerosis in men with SLE, we aimed to determine whether the prevalence and extent of asymptomatic coronary artery atherosclerosis are increased in men with SLE compared with age- and sex-matched controls, and to define the associated risk factors.

MATERIALS AND METHODS

Study participants. We studied 195 men including 95 ambulatory patients with SLE attending the Lupus Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in México City, and 100 age-matched controls selected among 2503 workers from the institute using a computer-generated randomization list. The study was approved by our hospital's institutional review board (IRE – 571), and all subjects provided written informed consent.

We included all male patients with SLE followed regularly in the lupus clinic from 2007–2013, age 18–60 years, meeting ≥ 4 American College of Rheumatology (ACR) classification criteria for SLE²². Patients and controls with history of cardio-cerebrovascular disease were excluded.

Coronary artery calcification assessment. All patients and controls had a standardized medical history, physical examination, and laboratory tests, including routine chemical analyses, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, lipoprotein(a) by cholesterol content, apolipoprotein B, homocys-

teine, and high-sensitivity C-reactive protein, measured in blood samples obtained after an overnight fast. In patients with SLE, the following auto-antibodies were measured: antinuclear, dsDNA, Sm, RNP/Sm, SSA/SSB, cardiolipin, β_2 -glycoprotein I, C3, and C4. Positivity was established according to the laboratory cutoff values.

All participants were assessed for CV risk factors including arterial hypertension (HTN; blood pressure $\geq 140/90$ mmHg), diabetes mellitus, family history of myocardial infarction (before age 55 and 65 yrs in first-degree male and female relatives, respectively), smoking status, dyslipidemia, body mass index (BMI; weight in kg/height² in m), waist circumference, and metabolic syndrome. The Framingham 10-year risk factor profile was calculated²³.

Standard of care for patients attending the lupus clinic includes appointments every 3–6 months with assessment of disease activity using the SLE Disease Activity Index 2000 update (SLEDAI-2K)²⁴, medications use and dose, comorbidities, and appointments to other medical specialists. Information about damage accrual using the Systemic Lupus International Collaborating Clinics Damage Index (SLICC/DI)²⁵, medical/surgical comorbidities, and CV risk factors is updated yearly.

Additional information was obtained from the medical chart, including age at SLE diagnosis and disease duration according to the ACR criteria at enrollment in the clinic, clinical manifestations during the course of the disease, length of followup, and SLE activity during the followup, measured using the adjusted-mean SLEDAI²⁶.

Multidetector computed tomography (CT). Coronary artery images were acquired in a 256-slice Multidetector CT system (Flash, Siemens) following the recommended scan acquisition measures²⁷. The best diastolic cardiac phase was selected for reconstruction of the images, which were analyzed in a dedicated Workstation using calcium score software (Calcium Scoring, Siemens). The software uses an attenuation threshold of 130 Hounsfield units and a minimum of 3 contiguous pixels for identification of a calcified lesion. Each focus exceeding the minimum criteria was scored with the algorithm originally developed by Agatston, *et al*²⁸. The total calcium score was determined by summing individual lesion scores from each of the left main, left anterior descending, left circumflex, and right coronary arteries. Two expert radiologists read all CT scans blinded to the SLE or control status.

Statistical analyses. Cumulative prevalence of coronary artery calcifications in patients with SLE was plotted in a Kaplan-Meier curve by means of time-series analysis of cross-sectional data. Coronary calcium scores were stratified into categories of 0, 1–100, 101–300, and > 300 ^{17,19}. Risk factors were summarized as median (minimum–maximum) or mean (SD), and absolute frequencies (%). Cumulative disease activity during the entire period of followup was summarized as SLEDAI-2K time-adjusted means²⁶. Moderate/severe activity was defined as SLEDAI-2K score ≥ 7 . Univariate comparisons of cases and controls were conducted by means of the Student t test or Mann-Whitney U test, and chi-square or Fisher's exact test, as appropriate. Multiple regression and logistic regression models were run to account for potential confounders. A 2-sided p value of 0.05 was considered statistically significant. When appropriate, 95% CI were determined. The STATA (Stata Corp.) version 12.0 statistical package was used.

RESULTS

Patients with SLE and control subjects were of Hispanic origin with mean age 34.7 (10.1) and 34.8 (9.7) years, respectively ($p = 0.97$). Disease duration at the start of the followup in the clinic was 0.49 (1.9) years, and the length of followup at screening for coronary artery calcifications was 7.8 (6.9) years.

The distribution of traditional CV risk factors showed that patients with SLE were more often hypertensive (39% vs 4%, $p < 0.001$), had higher levels of homocysteine (14.3 ± 10.1 vs 9.6 ± 3.0 mg/dl, $p < 0.001$), and less frequently had a

normal glomerular filtration rate (GFR; 84% vs 100%, $p < 0.001$) than control subjects; however, other risk factors were distributed similarly or occurred less frequently in patients with SLE (Table 1).

Coronary artery calcifications. Among the 195 participants, calcifications were detected in 24 (12%). The distribution of demographic variables and CV risk factors by the presence of coronary artery calcifications showed that men with calcifications were older, had a bigger waist circumference, HTN, diabetes, metabolic syndrome, higher levels of homocysteine, lower GFR, higher Framingham risk score, and had a diagnosis of SLE more often than males without calcifications ($p < 0.05$; Table 2).

In the multivariate analysis, these factors were independently associated with the presence of calcifications: age (OR 1.12, 95% CI 1.04–1.20), SLE diagnosis (OR 3.38, 95% CI 1.07–10.64), diabetes mellitus (OR 6.88, 95% CI 1.50–31.62), Framingham risk score (OR 1.12, 95% CI 1.00–1.23), and GFR (OR 0.98, 95% CI 0.96–1.00).

The prevalence of calcifications was higher in patients with SLE than in control subjects [18% vs 7%, respectively

(OR 2.89, 95% CI 1.07–8.65, $p = 0.02$)], and the median calcium score among those with calcifications was nonsignificantly higher in patients with SLE than in control subjects (68.5, range 4.6–576.8, and 7.7, range 1.1–140.2, respectively, $p = 0.32$). The extent of coronary artery calcification is shown in Table 3.

Calcifications were observed in patients starting at age 32 years compared to age 41 years in control subjects, and within 2.3 years of diagnosis (Table 4).

Factors associated with coronary artery calcifications in men with SLE. Patients with calcifications were older, had a bigger waist circumference, were current smokers, had higher systolic blood pressure, lower GFR, more frequent metabolic syndrome, higher Framingham risk score, longer disease duration, higher SLICC/DI score, higher cumulative dose of prednisone, and lower frequency of anti-dsDNA antibodies, than patients without calcifications ($p < 0.05$). No SLE variables (including clinical manifestations; autoantibodies; disease activity at entry, during the course of disease, or length of moderate-severe activity) were different. Besides higher cumulative dose of prednisone (57.5 vs 19.7 g,

Table 1. Demographic variables and cardiovascular risk factors in men with SLE and control subjects at screening for coronary artery calcifications. Data are expressed as mean (SD) or median (minimum–maximum), unless otherwise specified.

Variable	Patients with SLE, n = 95	Control Subjects, n = 100	p
Demographics			
Age, yrs	34.7 (10.1)	34.8 (9.7)	0.97
Education, yrs	13.3 (3.6)	13.9 (2.9)	0.31
Body mass index, kg/m ²	26.6 (5.8)	27.9 (4.2)	0.006
Waist circumference, cm	90.3 (14.5)	94.3 (11.2)	0.007
Coronary artery risk factors, n (%)			
Current smoking	18 (19)	23 (23)	0.59
Ever smoking	48 (51)	49 (49)	0.89
Hypertension [†]	37 (39)	4 (4)	<0.001
Systolic blood pressure, mm/Hg	115.8 (9.5)	113.4 (10.4)	0.03
Diastolic blood pressure, mm/Hg	74.5 (8.5)	76.7 (6.9)	0.03
Diabetes	8 (8)	4 (4)	0.24
Total cholesterol, mg/dl	184.2 (57.4)	199.1 (36.2)	<0.001
Low-density lipoprotein, mg/dl	112.4 (41.9)	121.5 (29.4)	0.007
High-density lipoprotein, mg/dl	39.1 (11.4)	48.9 (8.9)	0.001
Triglycerides, mg/dl	172.7 (117.7)	183.1 (110.8)	0.54
Glucose, mg/dl	89.7 (15.6)	105.9 (44.8)	<0.001
Apolipoprotein B, mg/dl	96.9 (30.6)	105.6 (22.3)	<0.001
Creatinine, mg/dl	0.93 (0.36–19.04)	0.95 (0.65–1.36)	0.66
eGFR (CKD-EPI), ml/min	105.0 (3.0–169)	103.5 (60–131)	0.83
eGFR < 60 ml/min, n (%)	15 (16)	0	<0.001
Homocysteine, mg/dl	14.3 (10.1)	9.6 (3.0)	<0.001
Ultrasensitive CRP, mg/l	4.96 (11.7)	2.4 (3.6)	0.06
MetS, n (%)	34 (36)	34 (34)	0.88
Framingham risk score	3 (2–25)	3 (2–18)	0.32
Coronary artery calcification, n (%) [‡]	17 (18)	7 (7)	0.03

[†] Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. [‡] Coronary artery calcification defined as total calcium score > 0 . SLE: systemic lupus erythematosus; MetS: metabolic syndrome; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Table 2. Demographic variables and cardiovascular risk factors at screening, in men with SLE and control subjects per the presence of coronary-artery calcification. Data are expressed as the mean (SD) or median (minimum–maximum), unless otherwise indicated.

Variable	Men with Calcification [†] , n = 24	Men without Calcification, n = 171	p
Demographics			
Age, yrs	44.9 (6.7)	33.3 (9.4)	< 0.001
Education, yrs	13.6 (3.7)	13.6 (3.3)	0.84
Body mass index, kg/m ²	27.8 (5.6)	27.2 (4.9)	0.53
Waist circumference, cm	96.5 (12.7)	91.7 (13.0)	0.03
Coronary artery risk factors			
Current smoking, n (%)	9 (38)	32 (18)	0.06
Past smoking, n (%)	14 (58)	77 (45)	0.28
Ever smoking, n (%)	15 (63)	82 (48)	0.28
Hypertension [‡] , n (%)	11 (46)	30 (18)	0.005
Systolic blood pressure, mm/Hg	119.6 (10.4)	113.8 (9.8)	0.006
Diastolic blood pressure, mm/Hg	78.3 (8.2)	75.2 (7.7)	0.06
Diabetes, n (%)	5 (21)	7 (4)	0.008
Total cholesterol, mg/dl	194.5 (48.6)	191.5 (48.2)	0.72
Low-density lipoprotein, mg/dl	115.9 (37.5)	117.2 (36.2)	0.79
High-density lipoprotein, mg/dl	39.2 (11.1)	41.9 (10.3)	0.25
Triglycerides, mg/dl	183.4 (71.2)	177.3 (119.0)	0.16
Glucose, mg/dl	122.2 (82.9)	94.6 (18.6)	0.29
Apolipoprotein B, mg/dl	103.6 (24.7)	101.1 (27.3)	0.59
Creatinine, mg/dl	0.98 (0.36–13.41)	0.93 (0.5–17.7)	0.18
eGFR (CKD-EPI), ml/min	88 (4–149)	105 (3–150)	0.003
eGFR < 60 ml/min, n (%)	5 (20)	10 (6)	0.03
Homocysteine, mg/dl	16.8 (15.3)	11.4 (6.1)	0.007
Ultrasensitive CRP, mg/l	4.9 (5.4)	2.9 (4.3)	0.02
MetS, n (%)	14 (58)	54 (32)	0.01
Framingham risk score	7.5 (2–25)	3 (2–16)	< 0.001
SLE, n (%)	17 (71)	78 (46)	0.03

[†] Coronary artery calcification defined as total calcium score > 0. [‡] Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. SLE: systemic lupus erythematosus; MetS: metabolic syndrome; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Table 3. Prevalence and extent of coronary artery calcifications in men with SLE and control subjects.

Variable	Patients with SLE, n = 95	Control Subjects, n = 100
Coronary artery calcification [†] , n (%)	17 (18)	7 (7)
OR 2.89 (95% CI 1.07–8.65), p = 0.02		
Median calcium score	68.5	7.7
Extent of coronary artery calcification, n (%)	Range 4.6–576.8	Range 1.1–140.2
0	78 (82)	93 (93)
> 0–100	13 (14)	5 (5)
> 100–300	3 (3)	2 (2)
> 300	1 (1)	0

[†] Coronary artery calcification defined as total calcium score > 0. SLE: systemic lupus erythematosus.

p < 0.001), no other medication showed positive association or preventing effect (Table 5).

In the multivariate analysis adjusting for disease duration, these were independently associated factors: age (OR 1.18, 95% CI 1.06–1.31), SLICC/DI score (OR 2.85, 95% CI 1.21–6.73), and cumulative dose of prednisone (OR 1.04, 95% CI 1.01–1.08).

DISCUSSION

Coronary artery calcifications occurred more frequently in men with SLE than in sex- and age-matched controls. In SLE, calcifications developed at a younger age, within 2.3 years of diagnosis, and were independently associated with increasing age, chronic damage, and cumulative dose of corticosteroids.

Table 4. Prevalence of coronary artery calcification in men with SLE and control subjects according to age and disease duration.

Variable	Men with SLE, n = 95		Control Subjects, n = 100	
	No. Patients	Coronary Artery Calcification†, n (%)	No. Subjects	Coronary Artery Calcification†, n (%)
Age, yrs				
≤ 20	8	0	3	0
21–30	30	0	39	0
31–40	28	5 (18)	28	0
41–50	21	8 (38)	22	5 (23)
51–60	8	4 (50)	8	2 (25)
Disease duration, yrs				
0–3	23	2 (9)	—	—
> 3–6	18	2 (11)	—	—
> 6	54	13 (24)	—	—

† Coronary artery calcification defined as total calcium score > 0. SLE: systemic lupus erythematosus.

In both study groups, mean age at calcification screening was < 35 years; patients with SLE had been followed regularly every 3–6 months, from 0.49 years of diagnosis and during 7.8 years of followup. Through the evolution, we were able to oversee CV risk factor accretion, course of disease activity, chronic damage accrual, comorbidities, use of medications, and cumulative dose of prednisone. In control subjects, CV risk factors were assessed through medical history including an ad-hoc questionnaire. Both groups were assessed for coronary artery calcifications using CT; therefore, we are confident about the accuracy of the independent variables and the outcome.

Patients with SLE more frequently had arterial HTN, lower GFR, and higher levels of homocysteine than did control subjects; however, no difference was observed in the distribution of smoking, diabetes, metabolic syndrome, and Framingham risk score. Further, higher among controls were BMI, waist circumference, LDL-C, glucose, and apolipoprotein B levels. Despite no clear difference in the distribution of traditional CV risk factors between groups, coronary artery calcifications occurred more frequently in SLE, emphasizing the notion of SLE as CV risk factor. Further, comparing the characteristics of all participants by the presence of coronary artery calcifications, calcium score was associated to older age, higher Framingham risk score, presence of diabetes mellitus, and SLE diagnosis; meanwhile, a higher GFR had a protective effect.

Among patients with SLE, older age, increasing chronic damage, and cumulative dose of prednisone were independent risk factors for coronary artery calcifications, after adjusting for disease duration. However, in the univariate analysis, other variables such as waist circumference, current smoking, systolic blood pressure, metabolic syndrome, lower GFR, higher Framingham risk score, and longer disease duration were associated. Distinctively, no disease manifestations, disease activity at any time during the disease course, or autoantibodies were identified as risk factors.

Our study shows that in men, as it has been reported in

women, SLE is an independent risk factor for developing premature atherosclerosis. In another study conducted in our center among 128 Hispanic females with SLE of recent onset at start of followup, mean age was 31.7 years, and mean disease duration 4.9 years at screening, while the prevalence of coronary artery calcifications was 6%. Therefore, in comparison to the 18% prevalence observed in men with SLE, the burden of coronary artery calcifications is higher in men than women (OR 3.27, 95% CI 1.35–7.94)²⁹.

Our results are consistent with those reported by Asanuma, *et al.* In their study, coronary artery calcifications occurred more frequently in patients with SLE and at a younger age than controls, and the prevalence increased with age. Their mean calcium score was identical to that of our study, and among patients younger than 60 years, most calcium scores ranged 1–100. SLE patients with calcification were more likely to be older and male, but no association was observed with other risk factors for atherosclerosis, markers of inflammation, or disease activity⁵.

Also, among 75 female patients with SLE, age 20–48 years, coronary artery calcifications were associated with increased age, disease duration, and cumulative dose of corticosteroids, but not with clinical manifestations, autoantibodies, disease activity, or chronic damage⁶.

In another study conducted among 152 women with SLE and 142 controls, the incidence and extent of calcifications were higher among patients with SLE. Calcifications were associated with increasing age, disease duration, CV risk factors, levels of homocysteine, and lower GFR, but not with inflammatory markers⁸. Two variables deserve closer attention: homocysteine concentration and lower GFR. In our study, both variables were associated with coronary artery calcifications in the univariate analysis of patients with SLE and control subjects. Lower filtration rate remained in the multivariate analysis, and was associated in the univariate analysis of SLE patients with and without coronary artery calcifications.

Traditional CV risk factors fail to predict half of coronary

Table 5. Analysis of men with SLE at screening, according to presence of coronary artery calcification.

Variable	SLE with Calcification [†] , n = 17	SLE without Calcification, n = 78	p
Demographics			
Age, yrs, mean (SD)	43.9 (7.1)	32.7 (9.5)	< 0.001
Education, yrs, mean (SD)	13.8 (3.8)	13.2 (3.6)	0.52
Body mass index, kg/m ² , mean (SD)	27.7 (6.1)	26.4 (5.7)	0.27
Waist circumference, cm	95.9 (14.0)	89.1 (14.4)	0.02
Higher waist*, n (%)	11 (65)	29 (37)	0.06
Coronary artery risk factors			
Current smoking, n (%)	7 (41)	11 (14)	0.02
Ever smoking, n (%)	11 (65)	37 (47)	0.29
HTN, n (%) [‡]	10 (59)	27 (35)	0.10
Systolic blood pressure, mm/Hg, mean (SD)	119.4 (7.5)	114.9 (9.7)	0.04
Diastolic blood pressure, mm/Hg, mean (SD)	77.1 (7.7)	73.9 (8.6)	0.09
Diabetes, n (%)	3 (18)	5 (6)	0.15
Total cholesterol, mg/dl, mean (SD)	182.5 (47.1)	184.5 (59.7)	0.99
Low-density lipoprotein, mg/dl, mean (SD)	108.3 (36.6)	113.3 (43.3)	0.65
High-density lipoprotein, mg/dl, mean (SD)	37.2 (11.8)	39.6 (11.3)	0.35
Triglycerides, mg/dl, mean (SD)	185.6 (68.9)	169.8 (126.2)	0.07
Glucose, mg/dl, mean (SD)	98.8 (29.8)	87.7 (9.2)	0.14
Apolipoprotein B, mg/dl, mean (SD)	96.1 (22.1)	97.1 (32.4)	0.69
Creatinine, mg/dl, median (min–max)	1.04 (0.36–13.41)	0.91 (0.42–19.04)	0.12
eGFR (CKD-EPI), ml/min, median (min–max)	85 (4–149)	108 (3–169)	0.02
eGFR < 60 ml/min, n (%)	4 (24)	10 (13)	0.25
Homocysteine, mg/dl, mean (SD)	18.9 (17.4)	13.3 (7.5)	0.16
Ultrasensitive CRP, mg/l, mean (SD)	5.6 (6.1)	3.6 (5.0)	0.10
MetS, n (%)	11 (65)	23 (29)	0.01
Framingham risk score, median (min–max)	5 (2–25)	3 (2–13)	0.003
SLE characteristics			
Age at diagnosis, yrs, mean (SD)	30.2 (10.2)	25.5 (8.9)	0.07
Disease duration, yrs, mean (SD)	13.7 (9.8)	7.1 (5.7)	0.01
SLEDAI adjusted mean (SD)	3.9 (2.5)	4.7 (2.8)	0.32
SLICC/DI score, mean (SD)	2.0 (1.7)	0.9 (1.2)	0.02
SLICC/DI > 0, n (%)	14 (82)	48 (62)	0.16
SLE criteria, n (%)			
Arthritis	12 (71)	62 (79)	0.52
Oral ulcers	5 (29)	23 (29)	1.00
Malar rash	8 (47)	29 (37)	0.58
Discoid rash	1 (6)	7 (9)	1.00
Photosensitivity	3 (18)	17 (22)	1.00
Serositis	4 (24)	19 (24)	1.00
Renal	10 (59)	52 (67)	0.58
Neurology	3 (18)	8 (10)	0.41
Hematology	11 (65)	48 (62)	1.00
Immunology	11 (65)	50 (64)	1.00
ANA	15 (88)	75 (96)	0.22
Autoantibodies profile, n (%)			
Anti-dsDNA antibodies	2 (12)	32 (41)	0.03
Anti-Sm antibodies	5 (29)	34 (44)	0.42
Anti-RNP/Sm antibodies	7 (41)	34 (44)	1.00
Anti-SSA antibodies	4 (24)	20 (26)	1.00
Anti-SSB antibodies	13 (76)	52 (67)	0.57
Antiphospholipid antibodies, n (%)			
IgM anticardiolipin antibodies	2 (12)	9 (12)	1.00
IgG anticardiolipin antibodies	4 (24)	15 (19)	0.74
IgM anti-β ₂ -GPI antibodies	2 (12)	7 (9)	0.66
IgG anti-β ₂ -GPI antibodies	4 (24)	12 (15)	0.48
Treatment			
Prednisone use, ever, n (%)	11 (65)	59 (76)	0.37
Cumulative dose of prednisone, g, median (min–max)	57.5 (8.5–454)	19.7 (0–114)	< 0.001
AZA use, ever, n (%)	13 (76)	40 (51)	0.07
CYC use, ever, n (%)	5 (29)	26 (33)	1.00
Anti-malarials, n (%)	11 (65)	46 (59)	0.79
Low-dose aspirin, n (%)	7 (41)	20 (26)	0.24

*Male > 90 cm, female > 80 cm. [†] Coronary artery calcification defined as total calcium score > 0. [‡] HTN defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; MetS: metabolic syndrome; ANA: antinuclear antibodies; HTN: hypertension; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; SLICC/DI: Systemic Lupus International Collaborating Clinics Damage Index; anti-β₂-GPI: apolipoprotein H; AZA: azathioprine; CYC: cyclophosphamide.

events in the general population³⁰; also, they do not fully explain the burden of atherosclerosis in SLE and other inflammatory diseases^{9,30,31}. Still, they are important and are a leading risk of premature atherosclerosis in SLE. The risk imposed by other factors such as high levels of homocysteine, SLE clinical manifestations, disease activity, or autoantibodies is uncertain, and a distinctive “SLE factor” is still unidentified⁸.

Inflammation plays a major role in the onset and progression of atherosclerosis. The search continues to identify inflammatory molecules that might lead the atherosclerotic process in SLE, with limited success^{8,29,32}.

Atherosclerosis is a process that takes place over time and results from the dynamic interplay of multiple factors. The relevance of these factors varies in different scenarios and times depending on patient characteristics such as age, sex, race, and disease duration. Because the effect of CV diseases on the morbidity and mortality of patients with SLE is growing, novel methods are needed to identify those patients who would benefit most from intensive primary prevention efforts. Expert panels have recommended testing for coronary artery calcifications in intermediate-risk individuals³³; as well as in asymptomatic men 45 to 75 years of age and asymptomatic women 55 to 75 years of age^{33,34}. Recommendations are less clear about screening for the many patients with SLE in the younger population, even though this population is still at risk of developing coronary artery calcifications and CV events.

As the prevalence and survival rate of men with SLE increase, it is important to know the characteristics of atherosclerosis in male patients. The age-adjusted prevalence rate of SLE in men in the United States is 12.8–14.7 per 100,000^{1,2}. Considering that the current US population is 324.5 million, and 49% are male, the number of men with SLE should be 20,353–23,374 (www.census.gov).

Until new knowledge is available, efforts to reduce the morbidity and mortality of CV diseases in patients with SLE should focus on strict control of CV risk factors, and optimum control of disease activity with the lowest possible dose of corticosteroids.

Our study has several limitations. We selected active workers from our institution as a control group instead of men from the general population. Whether the healthy worker effect influences our results need to be considered for their interpretation. We studied asymptomatic coronary atherosclerosis instead of clinical events; however, calcium score is a strong predictor of incident coronary heart disease beyond traditional risk factors¹⁹. The low prevalence of coronary artery calcifications in our study population might limit the strength of the results and conclusions, as well as the ability to identify other factors potentially associated with calcifications; nevertheless, their relevance should be less than the weight imposed by the factors identified. We did not study the presence of non-calcified coronary plaque; however, the

absence of calcified plaque conveys an extraordinarily low 10-year risk, irrespective of the number of traditional CV risk factors²¹. Serum inflammatory molecules implicated in the pathogenesis of atherosclerosis were not measured, because in a previous study we found no relationship with coronary artery calcification²⁹. This is a single-center study with limited ethnic variation; because the prevalence and extent of coronary artery calcifications varies across ethnic groups³⁵, one must be cautious about extrapolating these results to all male patients with SLE.

This is the first study, to our knowledge, to analyze the burden of coronary artery calcifications and associated risk factors in men with SLE within the early years of the disease, with a systematic followup during 7 years at a single center. The mild extension of coronary artery calcifications reflects the early stages of atherosclerosis in the study population.

Based on the results shown, we conclude that men with SLE are at an increased risk of coronary artery calcifications than age- and sex-matched controls. The increased risk is associated to older age, traditional CV risk factors, diabetes mellitus, lower GFR, and diagnosis of SLE. Among patients with SLE, the risk is associated with increasing age, increasing chronic damage, and cumulative dose of corticosteroids.

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