Peripheral Arterial Disease in Systemic Lupus Erythematosus: Prevalence and Risk Factors

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ABSTRACT. ***Objective.*** To analyze the prevalence of peripheral arterial disease (PAD) and cardiovascular (CV) risk factors in a cohort of patients with systemic lupus erythematosus (SLE) and to identify variables potentially related to PAD.

Methods. The study included 216 patients with SLE from the Lupus-Cruces prospective observational cohort. The ankle brachial index (ABI) was determined in each patient, with values < 0.9 considered diagnostic of PAD. Demographic and clinical variables, presence of traditional risk factors and CV events, cardiovascular risk calculated by Systematic Coronary Risk Evaluation (SCORE), and treatments received by each patient were analyzed.

Results. Ninety-two percent of patients were women. The mean age (SD) was 49 years (15), with a mean followup (SD) of 12 years (9). The prevalence of low ABI was 21%. CV risk factors were frequent: smoking, 30% of patients; high blood pressure, 32.7%; diabetes mellitus, 3.2%; hypercholesterolemia, 34.1%; and metabolic syndrome, 9.7%. The following variables were associated with low ABI in the univariate analysis: age ($p < 0.001$), hypertension ($p = 0.002$), diabetes ($p = 0.018$), hypercholesterolemia ($p = 0.018$), CV events ($p < 0.001$), SCORE ($p = 0.004$), cumulative dose of cyclophosphamide ($p = 0.03$), and fibrinogen levels ($p = 0.002$). In the multivariate analysis, the only independent variable in the final model was age (OR 1.04, 95% CI 1.02–1.07, $p < 0.001$), with a tendency for the presence of any vascular risk factor (diabetes, hypertension, hypercholesterolemia, or current smoking; OR 2.3, 95% CI 0.99–5.1, $p = 0.053$).

Conclusion. The prevalence of low ABI in patients with SLE is higher than expected. While the association with CV risk factors and vascular disease in other territories was strong, we could not identify SLE-specific variables independently associated with PAD. (First Release Jan 15 2014; J Rheumatol 2014;41:310–17; doi:10.3899/jrheum.130817)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS VASCULAR DISEASE HYPERTENSION
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Patients with systemic lupus erythematosus (SLE) have an increased prevalence of cardiovascular (CV) disease. The bimodal pattern of mortality proposed by Urowitz, *et al* in 1976 described a late peak of mortality mainly due to atherosclerotic heart disease[1]. In different series, the prevalence of symptomatic coronary artery disease (CAD) ranged from 6 to 10%[1,2,3,4]. Women younger than 55 years of age with SLE have a 5-fold to 8-fold higher risk of developing CAD compared to women in the general population[2]. The risk of hospitalization for stroke has been shown to be 2-fold higher in patients with SLE[3].

Premature atherosclerosis has been primarily related to traditional vascular risk factors[2,4]. However [and despite the higher prevalence of hypertension (HTN) and hypercholesterolemia in patients with SLE compared with the general population], traditional Framingham CV risk factors fail to fully explain the increased CV morbidity and mortality seen in SLE[5]. Several studies have found an association between premature atherosclerosis and some SLE-related factors, such as disease duration, steroid therapy, or irreversible organ damage[2,4,5,6].

Peripheral arterial disease (PAD) is frequently asymptomatic and can be difficult to diagnose[7]. The development of noninvasive, simple techniques with low intraobserver and interobserver variability, such as the ankle-brachial index (ABI), has facilitated the detection of subclinical PAD[8]. An ABI lower than 0.9 is diagnostic of PAD with 95–99% accuracy[9]. Moreover, a low ABI has been related to a higher incidence of myocardial infarction and stroke and higher

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mortality, both vascular and nonvascular, in studies in the general European and North American populations[10,11].

The incidence, risk factors, and consequences of PAD have not been well studied in patients with SLE. Given the high risk for atherosclerotic disease in patients with SLE, subclinical PAD is possibly frequent and underdiagnosed, with potential prognostic implications. We aimed to study the prevalence of PAD in the Lupus-Cruces cohort and to analyze the associated vascular and nonvascular risk factors.

MATERIALS AND METHODS

Study objectives. The primary objective in this cross-sectional study was to determine the prevalence of PAD in patients with SLE. The secondary objective was to identify factors potentially associated with PAD.

Study population and variables. Consecutive patients within the Lupus-Cruces longitudinal observational cohort, at the Autoimmune Diseases Unit, Hospital Universitario Cruces (a tertiary teaching center in Barakaldo, Spain, associated with the University of the Basque Country), were invited to participate in our study between January 2010 and June 2011. All patients fulfilled the 1997 classification criteria of the American College of Rheumatology[12]. The local institutional review board of the Hospital Universitario Cruces approved the study protocol in compliance with the Helsinki Declaration. All patients signed an informed consent at the time of enrollment.

Patients were routinely assessed every 3 to 6 months, unless clinical status demands more frequent visits. On the other hand, patients on longterm remission were seen on a yearly basis. At each followup visit, a number of clinical and immunological variables from every patient were routinely collected in a database: demographic characteristics (age, sex, race, year of diagnosis), SLE manifestations, autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatments received (corticosteroids, immunosuppressives, antimalarials, anticoagulants, etc.), complications of the disease and/or treatment. Date of death and cause of death were recorded when appropriate. This database was completed with CV variables: presence of CV risk factors [age, defined as more than 55 and 65 years in men and women, respectively; arterial HTN, defined as 2 consecutive measurements of at least 140/90 mmHg or antihypertensive therapy; diabetes mellitus (DM), defined as 2 consecutive fasting blood glucose determinations ≥ 126 mg/dl or treatment with antidiabetic drugs; hypercholesterolemia, defined as total blood cholesterol fasting levels > 200 mg/dl on 2 consecutive determinations or treatment with cholesterol-lowering drugs; metabolic syndrome according to the Adult Treatment Panel III definition[13]; and current or past smoking], degree of physical exercise (aerobic exercise 1 h/day, at least 3 days a week), presence of previous subclinical organ damage [left ventricular hypertrophy (LVH), presence of microalbuminuria], previous CV events (previous coronary events, heart failure, cerebrovascular disease, renal disease, PAD, or advanced retinopathy), and CV disease-related treatments (aspirin, statins). CV events were defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests: myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by computed tomography (CT) scanning or magnetic resonance imaging; cerebral transient ischemic attacks (TIA) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting < 24 h. CV risk stratification was performed using the European Vascular Risk Systematic Coronary Risk Evaluation (SCORE) scale for the Mediterranean population[14]. The Systemic Lupus International Collaborating Clinics damage index (SDI)[15] and the SLE Disease Activity Index (SLEDAI)[16] were calculated at the time of enrollment for each patient.

The size, weight, and waist and hip circumference were determined in each patient at the time of performing the ABI, along with calculation of the body mass index (BMI). ABI was performed in both legs to each patient in *ad hoc* scheduled visits, from January 2010 to June 2011. The MD2/SD2 Dopplex High Sensitivity Pocket Doppler was used for our study and all ABI were performed by the same 2 trained physicians working together with each patient. In every patient, 1 ABI was calculated for each leg, the lowest value being chosen. An ABI < 0.9 was considered abnormal.

To evaluate subclinical organ damage, the presence of microalbuminuria and LVH were tested. All patients collected an early morning urine sample to calculate the albumin/creatinine ratio. Data to calculate LVH were extracted from echocardiograms performed during a screening program for detecting pulmonary HTN in the whole Lupus-Cruces cohort[17].

Statistical analysis. The clinical descriptors of the cohort were generated, using means with SD, medians and ranges, or proportions. The total prevalence of PAD was calculated. The relation between the different SCORE categories and the normal/abnormal ABI was tested by McNemar test. To identify associations with PAD, the following independent variables were tested against the dependent variable "ABI lower than 0.9", using chi-square with Yates' correction or Student t-test: age at SLE diagnosis, age at the time of ABI, disease duration, sex, age as a vascular risk factor, abdominal obesity, metabolic syndrome, DM, HTN, hypercholesterolemia, smoking (current or past), any vascular risk factor (DM or HTN or hypercholesterolemia or current/past smoking), exercise, alcohol consumption, family history of premature CV disease, BMI, menopause, previous subclinical organ damage (LVH and microalbuminuria), previous CV events [ischemic heart disease and/or heart failure (IHD/HF), stroke, PAD], chronic renal failure, previous arterial thrombosis (stroke or IHD/HF or PAD), uric acid, vitamin D levels, previous lupus nephritis or antiphospholipid syndrome, anti-DNA, anti-Ro, anti-La, anti-U_1RNP, anti-Sm, and antiphospholipid antibodies (aPL; lupus anticoagulant and/or anticardiolipin antibodies at medium-high levels on at least 2 different determinations 12 weeks apart), SLEDAI, SDI, prednisone (cumulative dose and maximum dose ever received), hydroxychloroquine (yes/no and total dose), cyclophosphamide (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (no. mos taking treatment), or statins (no. mos taking treatment) and fibrinogen levels at the time of the ABI. Those variables with a p value ≤ 0.1 in the univariate analysis were subsequently included in a backward stepwise logistic regression model to identify independent associations with PAD.

All statistical analysis was done using the software SPSS 20.0.0 statistical package for Mac OS X (SPSS Inc.).

RESULTS

Demographic and SLE-related variables. Two hundred sixteen patients were studied; 200 were women (92%). Two hundred nine patients (96%) were white, with the remaining consisting of 3 Afro-Caribbeans, 2 Hispanics, and 2 Arabs. The mean (SD) age at SLE diagnosis was 36 years (15). The mean age at the time of the ABI study was 49 (15) years, with a mean (SD) followup after SLE diagnosis of 12 (9) years. The remaining clinical and therapeutic variables are shown on Table 1.

CV risk factors, target organ damage, and previous CV events. Traditional CV risk factors were frequent in our cohort (Table 2). As a whole, 162 patients (74.7%) had at least 1 traditional CV risk factor. In terms of CV risk, 205 patients (95%) had a SCORE between 0 and 4 and 11 patients (5%) had a SCORE ≥ 5, which reveals a high or very high CV risk.

LVH was present in 15 patients (7%) and microalbu-

Table 1. Demographic and clinical characteristics of the cohort (n = 216). Values are expressed as n (%) unless otherwise noted.

Age at study, yrs, mean (SD)	49 (15)
Age at diagnosis of SLE, yrs, mean (SD)	36 (15)
Sex: female	200 (92)
SLE duration, yrs, mean (SD)	12 (9)
Autoantibodies	
Anti-DNA	106 (48.8)
Anti-Ro	70 (32.3)
Anti-La	18 (8)
Anti-RNP	30 (13.8)
Anti-Sm	29 (13.4)
Antiphospholipid antibodies	75 (34.6)
Lupus nephritis	60 (27.6)
Antiphospholipid syndrome	21 (9.7)
SDI at ABI	
0	98 (45.2)
1	53 (24.4)
2	31 (14.3)
3	19 (8.8)
4	11 (5.1)
5	4 (1.8)
8	1 (0.5)
SLEDAI at ABI	
0	104 (48.1)
1–5	91 (42.2)
≥ 6	21 (9.7)
Use of prednisone: y/n	191/25
Average daily dose of prednisone, mg/d, mean (SD)	5.6
Use of hydroxychloroquine:y/n	193/23
Use of immunosuppressive drugs	
Cyclophosphamide: y/n	52/164
Mycophenolate: y/n	34/182
Azathioprine: y/n	64/152
Use of statins: y/n	73/143

ABI: Ankle-brachial index; SDI: Systemic Lupus International Collaborating Clinics damage index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 2. Prevalence of cardiovascular risk factors, organ damage, and cardiovascular events in the full cohort (n = 216). Values are expressed as n (%).

Age as risk factor	41 (18.9)
Family history	25 (11.5)
Current smoking	65 (30)
Smoking (ever)	109 (50.2)
Alcohol	26 (12)
No exercise	97 (44.9)
Abdominal obesity	73 (33.6)
DM	7 (3.2)
Hypertension	71 (32.7)
Hypercholesterolemia	74 (34.1)
MS	21 (9.7)
BMI	
Low weight	20 (9.3)
Normal weight	86 (39.8)
Overweight	69 (31.8)
Obesity	36 (16.6)
Morbid obesity	5 (2.3)
Any vascular risk factor (DM, HBP, DLP, or current smoking)	162 (74.7)
LVH	15 (6.9)
Microalbuminuria*	39 (19.8)
IHD/HF	6 (2.8)
Stroke	19 (8.8)
CRD	22 (10)
PAD	3 (1.4)
Advanced retinopathy	0 (0)
Menopause	103 (50.7)
SCORE	
0	141 (65)
1	31 (14.3)
2	22 (10.1)
3	5 (2.3)
4	7 (3.2)
5	5 (2.3)
6	2 (0.9)
7	2 (0.9)
8	2 (0.9)
Any vascular event (stroke, IHD/HF, PAD, or CRD)	26 (12)

* Total sample: 196 patients, DM: diabetes mellitus; HBP: high blood pressure; DLP: dyslipoproteinemia; MS: metabolic syndrome; BMI: body mass index; LVH: left ventricular hypertrophy; IHD/HF: ischemic heart disease and/or heart failure; CRD: chronic renal disease; PAD: peripheral arterial disease; ABI: ankle-brachial index; SCORE: Systematic Coronary Risk Evaluation.

minuria in 39 of 196 patients (20%); 6 patients (2.8%) had ischemic heart disease and/or heart failure, 19 patients (8.8%) had a stroke, and 3 (1.4%) had symptomatic PAD. Advanced retinopathy was not found in any patient. As a whole, 26 patients (12%) had a history of at least 1 vascular event. In addition, 22 patients (10%) had some degree of chronic renal disease, mostly as a consequence of lupus nephritis.

Frequency and associations of low ABI. Forty-six of the 216 patients studied (21%) had an abnormal ABI (≤ 0.9). Compared with those with normal ABI, patients with low ABI were older at study date (mean age 57 vs 47 years, respectively, $p < 0.001$), were older at SLE diagnosis (mean age 43 vs 34 years, respectively, $p = 0.001$), and had more frequently age as a CV risk factor (32% vs 15%, $p = 0.014$). Women with a low ABI were more often postmenopausal (66% vs 47%, $p = 0.03$). Also, these patients had more traditional CV risk factors such as DM (8.7% vs 1.8%, $p = 0.018$), HTN (52.2% vs 27.5%, $p = 0.002$), and hypercholesterolemia (50% vs 29.8%, $p = 0.018$), and had more previous CV events, including IHD/HF (8.7% vs 1.2%, $p = 0.006$), stroke (17.4% vs 6.4%, $p = 0.02$), and previous arterial thrombosis (ischemic heart disease, stroke or PAD; 28.3% vs 7.6%, $p < 0.001$) than patients with a normal ABI. Patients with low ABI had more frequently at least 1 CV risk factor (presence of HTN, diabetes, hypercholesterolemia, or smoking ever) compared with patients with normal ABI (89.1% vs 70.8%, respectively, $p = 0.011$; Table 3). An increasing proportion of patients with a low ABI was seen paralleling SCORE values ($p = 0.004$; Table 4).

Among SLE-related variables, only higher fibrinogen levels (425 vs 378 mg, $p = 0.002$) and a lower cumulative

Table 3. Relationship between low ABI and cardiovascular variables (univariate analysis). Values are n (%) unless otherwise noted.

	Low ABI, n = 46	Normal ABI, n = 170	p
Age at SLE diagnosis, yrs, mean (SD)	43 (17)	34 (14)	0.001
Age at study, yrs, mean (SD)	57 (15)	47 (14)	< 0.001
Disease duration, yrs, mean (SD)	14 (10)	12 (9)	0.245
Sex (female)	41/46 (89)	158/170 (93)	0.394
Age as a vascular risk factor	15/46 (32)	26/170 (15)	0.007
Abdominal obesity	20/46 (43)	53/170 (31)	0.173
Metabolic syndrome	5/46 (11)	16/170 (9)	0.988
DM	4/46 (8.7)	3/170 (1.8)	0.018
HTN	24/46 (52.2)	47/170 (27.5)	0.002
Hypercholesterolemia	23/46 (50)	51/170 (29.8)	0.018
Current smoking	15,746 (33)	50/170 (29)	0.18
Smoking ever	24/46 (52)	84/170 (49)	0.74
Any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking)	37/46 (80)	99/170 (58)	0.005
Any vascular risk factor (DM, HTN, hypercholesterolemia, or ever smoking)	41/46 (89.1)	120/170 (70.8)	0.011
No exercise	20/46 (43)	77/170 (45)	0.82
Alcohol	5/46 (11)	21/170 (12)	0.36
Family history of CV disease	6/46 (13)	19/170 (11.2)	0.93
BMI: mean (SD)	26.7 (5.3)	25.5 (5.5)	0.2
Postmenopausal status*	27/41 (66)	75/161 (47)	0.03
Microalbuminuria**	7/40 (17)	32/156 (20)	0.67
Left ventricular hypertrophy	5/46 (11)	10/167 (6)	0.252
IHD/HF	4/46 (8.7)	2/170 (1.2)	0.006
PAD	2/46 (4.3)	1/170 (0.6)	0.052
Stroke	8/46 (17.4)	11/170 (6.4)	0.02
Chronic renal disease	4/46 (9)	18/170 (11)	0.707
Previous arterial thrombosis (stroke, IHD/HF, or PAD)	13/46 (28.3)	13/170 (7.6)	< 0.001
Uric acid, mg/dl: mean (SD)	4.47 (1.2)	4.49 (1.7)	0.94
D vitamin levels, ng/ml: mean (SD)	25.6 (11.7)	29.1 (27.3)	0.414

* Data calculated on 200 women. ** Total sample: 196 patients. SLE: systemic lupus erythematosus; DM: diabetes mellitus; HBP: high blood pressure; DLP: hypercholesterolemia; PAD: peripheral arterial disease; IHD/HF: ischemic heart disease and/or heart failure; ABI: ankle-brachial index; HTN: hypertension; CV: cardiovascular; BMI: body mass index.

Table 4. Prevalence of low ABI in the different SCORE risk groups.

SCORE	Low ABI (%)
0	17/140 (12)
1	11/31 (35)
2	7/22 (35)
3	2/5 (40)
4	3/7 (43)
5	3/5 (60)
6	1/2 (50)
7	1/2 (50)
8	1/2 (50)

p = 0.004. SCORE: Systematic Coronary Risk Evaluation; ABI: ankle- brachial index.

dose of cyclophosphamide (1.15 vs 2.74 g, p = 0.03) were significantly identified in patients with a low ABI compared with those with a normal ABI (Table 5).

After the multivariate analysis, the only independent variables in the final model were the age at the time of the ABI (OR 1.04, 95% CI 1.02–1.07, p < 0.001). There was a tendency for the presence of any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking; OR 2.3, 95% CI 0.99–5.1, p = 0.053; Table 6).

DISCUSSION

The prevalence of PAD in the general population is not well known, with 25% of patients being symptomatic. PAD is associated with a high frequency of vascular disease in other territories, such as the coronary (with a 4-fold higher risk of suffering a myocardial infarction) and cerebral arterial beds (with a 2-fold to 3-fold increased risk of stroke)[18]. Further, PAD is associated with a 3-fold increased mortality, mainly due to a 6-fold increased risk of coronary death[19]. Thus, the diagnosis of PAD, even in asymptomatic patients, is important to prevent future vascular events. The main risk

Table 5. Relationship between low ABI and SLE variables (univariate analysis). Values are n (%) unless otherwise indicated.

	Low ABI, n = 46	Normal ABI, n = 170	p
Lupus nephritis	11/46 (24)	49/170 (29)	0.635
APS	5/46 (11)	16/170 (9)	0.767
Anti-DNA antibodies	21/46 (46)	85/170 (50)	0.721
Anti-Ro antibodies	13/46 (28)	56/170 (33)	0.67
Anti-La antibodies	3/46 (6)	15/170 (9)	0.616
Anti-RNP antibodies	4/46 (9)	25/170 (15)	0.414
Anti-Sm antibodies	5/46 (11)	24/170 (14)	0.742
aPL	13/46 (28)	61/170 (36)	0.429
SLEDAI: mean (SD)	2 (3)	2 (3)	0.062
SLEDAI categorical:			0.663
0	80 (77)	24 (23)	
1–5	72 (79)	19 (21)	
≥ 6	18 (86)	3 (14)	
SDI: mean (SD)	1.26 (1.3)	1.09 (1.4)	0.453
Prednisone therapy ever	42/46 (91)	149/170 (88)	0.49
Total dose of prednisone, g, mean (SD)	16 (18.6)	23.8 (63.4)	0.678
Maximum dose of prednisone, g, mean (SD)	28.7 (26.2)	26.7 (26.3)	0.644
Hydroxychloroquine ever	40/46 (87)	153/170 (90)	0.553
Total dose of hydroxychloroquine, g, mean (SD)	432.3 (476.8)	409.7 (518.3)	0.79
Cyclophosphamide cumulative dose, g, mean (SD)	1.15 (3.3)	2.74 (6.9)	0.03
Aspirin, mos, mean (SD)	59 (66)	41 (66)	0.104
Statins, mos, mean (SD)	33 (53)	17 (40)	0.069
Anticoagulation, mos, mean (SD)	12 (37)	11 (41)	0.816
Fibrinogen, mg/dl, mean (SD)	425 (94.3)	378 (90.2)	0.002

SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ABI: ankle-brachial index; SDI: Systemic Lupus International Collaborating Clinics damage index.

Table 6. Variables associated with a low ABI (multivariate analysis).

	OR	95% CI	p
Age at study, yrs	1.04	1.02–1.07	< 0.001
Any vascular risk factor (DM, HTN, hypercholesterolemia, or current smoking)	2.3	0.99–5.1	0.053

ABI: ankle-brachial index; DM: diabetes mellitus; HTN: hypertension.

factors for PAD in the general population are smoking, DM, and arterial HTN. ABI testing is recommended in patients with intermittent claudication, in asymptomatic individuals older than 70 or older than 50 with vascular risk factors, and in patients with a Framingham risk score up to 10%, with absence of pedial pulses and/or presence of femoral bruits[20].

We found a high prevalence of mostly asymptomatic PAD in patients with SLE (21%). This prevalence is 10-fold higher than expected according to a recent Spanish population-based cross-sectional survey of 6262 individuals, which showed a 2.1% frequency of an ABI < 0.9 in the subgroup of women 45 to 54 years of age[21]. On the other hand, the frequency of symptomatic PAD in our cohort (1.3%) was similar to that found in the Toronto Lupus cohort (2%)[22].

Few have studied the prevalence of subclinical PAD in patients with SLE. One study from London of 91 patients with SLE younger than 55 years was designed to detect early signs of atheroma by using ABI, whose abnormal cutoff value was set at 1. The authors identified 37% of patients with PAD. Age was the only variable associated with a low ABI[23]. The lower prevalence of abnormal ABI found in our study could be explained in part by the lower cutoff we used, 0.9 instead of 1, according to current guidelines[20].

In a case-control study of 32 Chinese women with SLE who had no previous CV disease or DM, designed to study the correlation between arterial stiffness and disease activity, the authors did not report any cases with an abnormal ABI[24]. Another study of Chinese patients from Taiwan found a 4% frequency of abnormal ABI. That study was focused on the relation between homocysteine and brachial-ankle pulse wave velocity and no specific associations with ABI were sought[25]. The same group studied arterial stiffness by pulse wave velocity in 83 patients with SLE. An ABI was performed on the whole cohort, with 24% of them being abnormal; however, variables potentially related with a low ABI were not analyzed[26].

Like the London study, we found an association between the presence of PAD and age, both at the time of the study

and at SLE diagnosis[23]. The presence of menopause was also associated with a low ABI in the univariate analysis. The association between arterial events and the age at SLE diagnosis has been consistently described[2,4,27,28,29]. An association between CV events and menopause has been found as well[2].

Our study also revealed a strong association between PAD and traditional CV risk factors (DM, HTN, hypercholesterolemia, smoking, and SCORE scale), which persisted as a tendency in the multivariate analysis. A relation with the presence of previous CV events (IHD/HF, stroke, and previous arterial thrombosis) was also seen. Other authors have found associations with some, but not all, vascular risk factors. Petri, *et al* found a relation with serum cholesterol levels and HTN, but not with smoking or DM[4]. Manzi, *et al* described an incidence of myocardial events in women with SLE higher than expected in a population of women of similar age, according to the Framingham Study Cohort[2]. An association with hypercholesterolemia was seen, but not with other classic vascular risk factors[2]. Urowitz, *et al* found a relation between CV events (myocardial infarction, angina, TIA, stroke, PAD, and sudden death) and hypercholesterolemia, smoking, and HTN, but not with DM[30].

Other groups found associations of CV events with longer duration of SLE[2,4], positivity for aPL[27], Raynaud phenomenon, renal disease, neuropsychiatric disease, and vasculitis[30]. In contrast, we found no associations with most SLE-related factors, such as the autoantibody profile, disease activity, chronic organ damage, or treatment with prednisone or antimalarials. In the univariate analysis, higher fibrinogen levels and lower cumulative doses of cyclophosphamide were found in the low ABI group. Despite the loss of statistical significance of both variables in the multivariate analysis, the effect of chronic inflammation in the vascular endothelium is suggested. Accordingly, those therapies suppressing inflammation could have a beneficial effect.

However, studies analyzing the effects of immunosuppressive and antimalarial therapy on vascular disease have obtained heterogeneous results. Urowitz, *et al*[30] found an association between CV events and steroid use as a dichotomic "ever/never" variable, but not with the cumulative dose or the duration of treatment. Surprisingly, antimalarials and immunosuppressive drugs were used more frequently in the group of patients with CV events. Manzi, *et al*[2] and Petri, *et al*[4] found an association of CV disease with longer duration of corticosteroid use. Roman, *et al*[31] identified several variables associated with the presence of plaque: age, disease duration, and damage increased the risk, while positivity for anti-Sm and therapy with hydroxychloroquine and cyclophosphamide had a protective effect. A higher proportion of patients taking prednisone and a higher 5-year mean daily dose of prednisone were seen among patients without plaque. In a Brazilian study[32], hydroxychloroquine was not protective, while cyclophosphamide, methylprednisolone pulses, and the daily dose of prednisone were associated with a lower frequency of plaque. Interestingly, the duration of prednisone therapy was directly related to the presence of plaque, suggesting a somewhat dual effect of glucocorticoids. Such effect was also found in a study of pediatric patients with SLE in whom a beneficial effect of prednisone doses of 0.15–0.40 mg/kg/d on the carotid intima-media thickness was found; however, lower and higher doses were both associated with a higher intima-media thickness[33]. A direct effect of the cumulative dose of prednisone, both unadjusted and adjusted for Framingham risk factors, on the presence of carotid plaque was reported by Doria, *et al*[34] and similar results were obtained by Romero-Diaz, *et al* in Mexico[35].

These heterogeneous results may actually reflect the complex relation between disease activity, drug-associated side effects, and vascular disease. It is possible that a certain degree of immunosuppressive therapy protects from endothelial damage by controlling inflammation, but the proatherosclerotic effects of immunosuppressive drugs, particularly glucocorticoids, may prevail beyond a certain threshold. In addition, it is almost impossible to separate the strong association between SLE severity and more intensive immunosuppressive therapy. Lastly, a number of different endpoints have been used, from crude clinical vascular events to a wide range of noninvasive tests such as carotid ultrasound, CT scan, or arterial stiffness calculations, which can have different clinical implications. Thus, many questions about the effect of SLE therapy on vascular disease are still unresolved.

On the other hand, the effect of traditional CV risk factors on vascular disease in patients with SLE is clear. We found a prevalence of PAD in patients with SLE 10-fold higher than expected[21]. Up to 50% of our cohort was overweight, compared with 39% of the Spanish general population[36]. Thirty-four percent had hypercholesterolemia, compared to 50.5% of individuals in the Spanish general population[37]. The prevalence of HTN in the Spanish general population is 35%, similar to the 33% frequency seen in our patients[38]. However, the age range in epidemiological studies is 18 to 80 years, while the mean age of our cohort was 36 years. This suggests that hypercholesterolemia, HTN, and other vascular risk factors appear earlier in patients with SLE, with the expected clinical effect on the development of vascular disease.

This study has several limitations. First, this is a cross-sectional study, with a wide heterogeneity in variables such as the age, SLE duration, and degree of organ damage. The lack of statistical significance of some SLE-related variables identified in other studies may be partially explained by the confounding effects of this heterogeneity. Eighty-nine percent of our cohort was taking antimalarials, which makes it very difficult to analyze the actual effect of

these drugs, given the lack of a sizable comparison group not taking the therapy. However, the duration of therapy was neither directly nor inversely associated with PAD, remarking that the relation of antimalarials and atherosclerosis is far from clear[39]. The complex relationship between glucocorticoids and arterial disease has already been discussed. In our study, we only considered the cumulative and maximum dose of prednisone received. Given the variation in the time of followup of the individual patients, these glucocorticoid-related variables may not be optimal to analyze the influence of prednisone on PAD. Finally, the lack of a control group without SLE precluded the complete analysis of most SLE-related variables. Likewise, the prevalence of PAD in the general population, as measured by low ABI, was obtained from other studies in the Spanish population, and not directly calculated in a control group of our area. Regarding the effects of SLE activity on ABI, our study is limited by the low number of patients with a SLEDAI ≥ 6 at the time of the study. Also, previous SLEDAI scores were not analyzed. Therefore, we cannot exclude an effect of persistent severe SLE activity on the development of PAD.

On the other hand, this is the first study analyzing the incidence of PAD in patients with SLE using a validated diagnostic technique and a working definition in accordance with current international guidelines. In our descriptive study, we found a high prevalence of PAD in patients with SLE, which was asymptomatic in the vast majority of cases. The clinical implications of our data will be further clarified by future studies and by the longitudinal followup of our cohort.

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