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Predictors of peripheral arterial disease in SLE change with patient's age

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ABSTRACT

Objective: To analyse the differential influence of risk factors of peripheral artery disease (PAD) according to age in patients with SLE.

Methods: 216 patients from the Lupus-Cruces cohort were divided in three age groups: ≤34 years, 35–49 years and ≥50 years. A low ankle–brachial index defined PAD. Significant variables were identified by univariant and multivariant analysis in each age group.

Results: Different factors were identified in different age groups: antiphospholipid antibodies/antiphospholipid syndrome and glucocorticoids in patients ≤34 years; in patients 35–49 years old, hypertension was the only statistically significant predictor, although a trend was observed for fibrinogen levels; a trend was observed for hypercholesterolaemia in those ≥50 years.

Conclusions: Age may modulate the influence of risk factors for PAD in patients with SLE.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of late mortality in patients with SLE.[1] The incidence of CVD has progressively increased within the last decades.[2] CVD can present as coronary artery disease (CAD), cerebrovascular disease and peripheral artery disease (PAD), the first two ones being best studied.[3] The underlying atherosclerotic process can be accelerated by different mechanisms, including inflammation, SLE treatments and traditional cardiovascular risk factors.[3]

Age is the most important unchangeable cardiovascular risk factor, both in the general population and in patients with lupus.[4 5] Indeed, in a previous study in our SLE cohort, age was the only independent predictor of PAD.[6] In a nationwide population-based cohort study in Taiwan, younger (≤34 years) patients with SLE were at a higher risk of symptomatic PAD.[7] In a Swedish population-based study, an increased risk of myocardial infarction and stroke was demonstrated among female patients with SLE compared with the general population. Of note, this extra risk was highest among women aged 40–49 years.[8]

Thus, it is possible that the influence of risk factors, either cardiovascular or SLE-related, varies depending on the age of patients. To test this hypothesis, we aimed to study the influence of risk factors for PAD in different age groups of patients with SLE.

MATERIALS AND METHODS

Study objectives

The objective of this cross-sectional study was to analyse the differential influence, according to age, of several variables in the presence of PAD, defined as a low ankle–brachial index (ABI). Patients were divided in three groups according to age at the time of the ABI, as proposed by Chuang *et al*:[7] ≤34 years (group 1), 35–49 years (group 2) and ≥50 years (group 3).

Study population

Data from the 216 patients who participated in our previous study[6] were further analysed. Detailed characteristics of this population and the variables studied are available.[6] The local institutional review board of the Hospital Universitario Cruces approved the study protocol (CEIC E09/07) in compliance with the Helsinki Declaration. All patients signed an informed consent at the time of enrolment.

Statistical analysis and variables

In order to identify associations with PAD, the following independent variables were tested in each age group against the dependent variable, 'ABI lower than 0.9', using χ^2 with Yate's correction or Student's t-test, as appropriate: age at SLE diagnosis, disease duration, gender, abdominal obesity (≥102 and ≥88 in men and women, respectively), metabolic syndrome according to Adult Treatment Panel III definition,[9] diabetes mellitus (DM), arterial hypertension (HTN), dyslipidaemia, smoking (current or past), any vascular risk factor (DM or HTN or

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dyslipidaemia or current/past smoking), exercise, alcohol consumption, family history of premature CVD, body mass index, menopause, previous subclinical organ damage (left ventricular hypertrophy and microalbuminuria), previous CVD (ischaemic heart disease and/or heart failure (IHD/HF), stroke, PAD), chronic renal failure, previous arterial thrombosis (stroke or IHD or PAD), uric acid, vitamin D levels, previous lupus nephritis or antiphospholipid syndrome (APS), anti-DNA, anti-Ro, anti-La, anti-U1RNP, anti-Sm, and antiphospholipid antibodies (aPL) that include lupus anticoagulant and/or anticardiolipin antibodies at medium–high levels on at least two different determinations 12 weeks apart, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at the time of diagnosis, SLEDAI at the time of ABI, SLICC/ACR Damage Index (SDI) at the time of ABI, prednisone (cumulative dose, maximum dose ever received, average daily dose <7.5 or ≥7.5), hydroxichloroquine (yes/no and cumulative dose), cyclophosphamide (cumulative dose), mycophenolate (cumulative dose), azathioprine (cumulative dose), low-dose aspirin (number of months on treatment), anticoagulants (number of months on treatment), statins (number of months on treatment) and fibrinogen levels at the time of the ABI.

Those variables with a value of p ≤0.1 in the univariate analysis were subsequently included in a backward stepwise logistic regression model to identify independent associations with PAD for each age subgroup.

All statistical analyses were done using the software SPSS V.20.0 statistical package for MAC OS X (SPSS).

RESULTS

Demographic and SLE-related variables

Two hundred patients (92%) were women. Two hundred and nine patients (96%) were Caucasians of European origin, with the remaining consisting of three Afro-Caribbeans, two Hispanics and two Arabs. The mean (SD) age at SLE diagnosis was 36 years (15). The mean (SD) age at the time of the ABI study was 49 (15) years, with a mean (SD) follow-up after SLE diagnosis of 12 (9) years.

A total of 37 patients were included in group 1, 84 patients in group 2 and 95 patients in group 3. The distribution of traditional cardiovascular risk factors and SLE-related factors in the three age groups is detailed in table 1.

Frequency and associations of low ABI

The prevalence of PAD increased with age: 3/37 (8.1%) in group 1, 12/84 (14.2%) in group 2 and 31/95 (32.6%) in group 3. The variables associated with PAD in each age group are shown in table 2: APS, aPL and cumulative prednisone dose in group 1; DM, hypertension, average daily dose of prednisone <7.5 mg/day, abdominal obesity and fibrinogen levels in group 2; and vitamin D levels, hypercholesterolaemia, any vascular risk factor (DM or hypertension or hypercholesterolaemia or current/past smoking), ischaemic heart disease, aPL, previous arterial thrombosis, cumulative mycophenolate mofetil dose and average daily dose of prednisone <7.5 in group 3.

The final independent predictors of low ABI are shown in table 3. In group 1, the logistic regression

Table 1 Traditional and SLE-related cardiovascular risk factors in different age groups

	Group 1 (≤34 years)	Group 2 (35–49 years)	Group 3 (≥50 years)
HTN, n/N (%)	4/37 (10.8)	20/84 (23.8)	47/95 (49.4)
DM, n/N (%)	0/37 (0)	3/84 (3.5)	4/95 (4.2)
DLP, n/N (%)	3/37 (8.1)	20/84 (23.8)	51/95 (53.6)
Current smoker, n/N (%)	15/37 (40.5)	28/84 (33.3)	22/95 (23.1)
Smoker (ever), n/N (%)	18/37 (48.6)	49/84 (58.3)	41/95 (43.1)
Family history, n/N (%)	2/37 (5.4)	10/84 (11.9)	13/95 (13.6)
Abdominal obesity, n/N (%)	10/37 (27)	25/84 (29.7)	38/95 (40)
BMI, n/N (%) overweight–obesity	13/37 (35.1)	44/84 (52.3)	52/95 (54.7)
Sedentary lifestyle, n/N (%)	20/37 (54)	35/84 (41.6)	42/95 (44.2)
Any vascular risk factor, n/N (%)	22/37 (59.4)	59/84 (70.2)	80/95 (84.2)
MS, n/N (%)	3/37 (8.1)	6/84 (7.1)	12/95 (12.6)
APS, n/N (%)	2/37 (5.4)	10/84 (11.9)	9/95 (9.4)
aPL, n/N (%)	14/37 (29.7)	27/84 (32.1)	33/95 (34.7)
Lupus nephritis, n/N (%)	12/37 (32.4)	30/84 (35.7)	18/95 (18.9)
SLEDAI at dx, mean (SD)	9.83 (7.8)	8.15 (5.3)	6.1 (3.9)
SLEDAI at ABI, mean (SD)	3.08 (3.7)	2.05 (2.9)	1.5 (2.2)
SDI at ABI, mean (SD)	0.4 (0.8)	0.98 (1.2)	1.5 (1.5)
Age at SLE dx, years, mean (SD)	21.4 (6.1)	30.2 (9.2)	47.4 (15.6)
Disease duration, years, mean (SD)	6.2 (5.3)	11.7 (8.5)	15 (10.5)

Any vascular risk factor: DLP, hypercholesterolaemia; HTN, DM, dyslipidaemia or smoking exposed. ABI, ankle–brachial index; aPL, antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant); APS, antiphospholipid syndrome; BMI, body mass index; DM, diabetes mellitus; dx, diagnosis; HTN, arterial hypertension; MS, metabolic syndrome according to ATPIII.

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Table 2 Univariate analysis showing variables with p<0.1

	Low ABI	Normal ABI	p Value
Group 1 (≤34 years)	N=3	N=34	
APS, n/N (%)	2/3 (66)	0/34 (0)	0.005
aPL, n/N (%)	3/3 (100)	11/34 (32.3)	0.047
Cumulative prednisone, g, mean (SD)	21.25 (1.89)	7.70 (1.08)	0.058
Group 2 (35–49 years)	N=12	N=72	
DM, n/N (%)	2/12 (16.6)	1/72 (1.3)	0.052
HTN, n/N (%)	6/12 (50)	14/72 (19.4)	0.021
Average prednisone <7.5 mg/day, n/N (%)	11/11 (100)	50/68 (73.5)	0.046
Abdominal obesity, cm, mean (SD)	90.46 (14.9)	82.50 (12.2)	0.047
Fibrinogen levels, mg/dL, mean (SD)	454 (100)	388 (83.2)	0.021
Group 3 (≥50 years)	N=31	N=64	
Vitamin D levels, ng/mL, mean (SD)	22.2 (8.7)	35.9 (41.4)	0.018
Hypercholesterolaemia, n/N (%)	21/31 (67.7)	30/64 (46.8)	0.056
Any vascular risk factor (ever smoking), n/N (%)	30/31 (96.7)	50/64 (78.1)	0.015
Any vascular risk factor (current smoking), n/N (%)	28/31 (90.3)	44/64 (68.7)	0.023
Ischaemic heart disease, n/N (%)	4/31 (12.9)	2/64 (3.1)	0.086
aCL, n/N (%)	4/31 (12.9)	24/64 (37.5)	0.011
aPL, n/N (%)	6/31 (19.3)	27/64 (42.1)	0.028
Arterial thrombosis, n/N (%)	11/31 (35.4)	11/64 (17.1)	0.047
Cumulative MMF, g, mean (SD)	0 (0)	111 (442.8)	0.049
Average prednisone <7.5 mg/day, n/N (%)	28/30 (93.3)	48/63 (76.1)	0.038

ABI, ankle–brachial index; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant); APS, antiphospholipid syndrome; DM, diabetes mellitus; HTN, arterial hypertension; MMF, mycophenolate mofetil.

Table 3 Variables associated with a low ABI in different age groups (multivariate analysis)

Variables	OR	95% CI	p Value
Group 1			
N/A			
Group 2			
Hypertension	4.61	1.15 to 18.44	0.031
Group 3			
Hypercholesterolaemia	2.49	0.97 to 6.4	0.057

ABI, ankle–brachial index; N/A, not applicable.

model could not be built due to the absolute absence of any patients with APS in the subgroup with normal ABI and the 100% frequency of aPL positivity among those with abnormal ABI; thus, the results of the univariate analysis could not be adjusted. In group 2, hypertension was the only statistically significant predictor, although a trend was observed for fibrinogen levels. In group 3, a trend was observed for hypercholesterolaemia.

DISCUSSION

Age is among the most important cardiovascular risk factors; indeed, many of the cardiovascular risk estimation models are actually based on age.[4 5] In a cohort of more than 3.6 million individuals undergoing self-referred screening for CVD (ABI, carotid duplex ultrasound and abdominal ultrasound), the prevalence of any vascular disease increased progressively after 40 years of age: from 2% in those aged 40–50 years to 13% among those aged 71–80 years. After adjusting for traditional risk factors, each additional decade of life doubled the risk for vascular disease (OR 2.14 for PAD).[10]

Moreover, the differential influence of cardiovascular risk factors changes throughout life. In the general population, the Framingham study found that the relative effect of systolic, diastolic and pulse pressure changed with age. In patients younger than 50 years, diastolic blood pressure was the strongest predictor of coronary heart disease (CHD) risk; in those aged 50–59 years old, all three variables contributed equally to CHD risk; among those older than 60 years, pulse pressure was the strongest predictor.[11]

Our results suggest that age may modulate the effect of risk factors for CVD also in patients with SLE. aPL/APS and higher glucocorticoid load seem to increase the risk of PAD in younger patients, although a multivariant analysis could not be performed. In group 2, an average daily dose of prednisone <7.5 mg was associated with PAD in the univariate but not in the multivariate analysis. Moreover, since more than 75% of patients in this age group were taking low-dose prednisone, this result is likely to be misleading. As age increased, more traditional risk factors such as hypertension and hypercholesterolaemia played a significant role. We identified factors associated with PAD (and, probably, by extension with CVD) hidden by the large influence of age. This could be particularly important among younger patients, in whom the prevalence of arterial disease was low, however very much unrelated to classical cardiovascular risk factors.

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This study has a number of limitations, which have been already acknowledged.[6] This is a cross-sectional study, with different disease duration among patients. This makes it difficult to fully address the effects of some time-varying variables such as glucocorticoid exposure, lupus activity and cardiovascular risk factors. In addition, almost 90% of our cohort was on hydroxychloroquine, which precludes analysis of the actual effect of this drug. On the other hand, the sizeable number of patients has allowed a differential analysis per different age groups using a large variety of demographic, cardiovascular, lupus-related and therapeutic variables. This is, to our knowledge, the first study of this kind.

Based on our results, a number of practical considerations can be made. First, it is important to regularly check patients with lupus for the presence of aPL, especially in the early phases of the disease, given the possible association with PAD in young patients with SLE. We have previously shown that aPL increase the risk of damage in SLE,[12] particularly by the occurrence of thrombotic events.[13] Since the addition of low-dose aspirin seems to be protective in aPL-positive patients with SLE according to a recent systematic review,[14] the detection of persistently positive aPL should call for early antiplatelet therapy. Second, the doses of prednisone should be reduced as much as possible, especially in young patients, given the possible association with PAD in this group and, in general, with damage in patients with SLE.[15] Third, especial attention should be paid to controlling traditional cardiovascular risk factors, especially in older patients.

Contributors J-GE: substantial contributions to the conception, design of the work, acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IV: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JN: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IR-A: Substantial contributions to the analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GR-I: Substantial contributions to the conception and design of the work; analysis and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The local institutional review board of the Hospital Universitario Cruces approved the study protocol (CEIC E09/07).

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