Cumulated organ damage is associated with arterial stiffness in women with systemic lupus erythematosus irrespective of renal function

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Abstract

Objective

To determine whether there is an association between cumulated organ damage and arterial stiffness in women with systemic lupus erythematosus (SLE) with normal renal function and without renal damage.

Methods

Eighty-eight SLE women with normal renal function and without renal damage, and 102 sex- and age-matched controls with no history of coronary heart disease or peripheral arterial disease were studied. Cumulated organ damage and arterial stiffness were measured using the SLICC/ACR Damage Index (SDI) and pulse wave velocity (PWV), respectively. Patients were categorised as with (SDI ≥1) or without cumulated organ damage (SDI=0) and bivariate analyses were performed to compare both groups. A multivariate logistic regression was carried out to analyse the independent factors associated with cumulated organ damage. A multiple linear regression analysis was used to investigate the correlation between SDI and PWV, adjusted for appropriate confounders.

Results

PWV was significantly higher in patients with respect to controls (p=0.007). Also, patients with SDI ≥1 had significantly higher PWV than those with SDI=0 (p=0.007). In the multivariate analysis, cumulated organ damage was significantly associated with PWV (p=0.006) and obesity (p=0.003). Furthermore, PWV correlated with SDI after adjustment for age, SLE duration, systolic blood pressure, body mass index, renal function, prednisone and homocysteine (r=0.283, p=0.011). Patients with increased PWV were more likely to have organ damage (SDI ≥1) than those with normal PWV (67% vs. 36%, p=0.023).

Conclusion

Cumulated organ damage was found to be independently associated with the arterial stiffness in SLE women without renal involvement.

Key words

renal damage, SDI, arterial stiffness, pulse wave velocity, cardiovascular diseases, systemic lupus erythematosus.

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Introduction

The survival rate of patients with systemic lupus erythematosus (SLE) has improved over recent decades. This increased longevity means that these patients may develop cumulated organ damage throughout the disease as a result of ongoing inflammatory insults, the presence of comorbidities and prolonged exposure to treatments. The Systemic Lupus International Collaborating Clinics/American Collage of Rheumatology Damage Index (SDI) is a validated instrument designed to measure irreversible organ damage after SLE diagnosis, regardless of the cause or attribution (1). This is an important tool for the assessment of patients with SLE since it is closely related to the prognosis (2) and the health-related quality of life (3).

Cardiovascular diseases (CVD) are one of the leading causes of mortality in SLE and one of the contributors to organ damage. Few epidemiological studies have reported that increased SDI may contribute to the development of CVD (4). In addition, the association between cumulated organ damage and atherosclerosis, especially arterial stiffness, has been scarcely investigated (5, 6). Renal disease has been found to be a major contributor to both organ damage (1) and arterial stiffness in patients with SLE (6). Nevertheless, the relationship between arterial stiffness and organ damage has never been studied in SLE patients with normal renal function and without renal damage.

The aim of this study was to determine whether in this subgroup of patients there was an association between organ damage and arterial stiffness, measured by carotid-femoral pulse wave velocity (PWV), that is considered an early surrogate marker of vascular risk in patients with SLE (7).

Materials and methods

Consecutive non-pregnant women with SLE aged ≥18 years old attending our Unit and a matched control group for sex and age were invited to participate. We excluded patients with chronic kidney disease (see Appendix) and with renal damage as defined by the items in the renal domain of the SDI (1). Other exclusion criteria were: less than 1 year of follow-up, morbid obesity that hinders PWV measurement, and a history of myocardial infarction, angina, coronary artery by-pass or peripheral arterial disease, which correspond with specific items in the cardiovascular and peripheral vascular domains of the SDI (1). All participants were white. The study was approved by the Institutional Review Board of our hospital. All subjects gave written informed consent.

Patients were assessed for socio-demographic, anthropometric and clinical data, CVD risk factors and medications. Fasting blood samples for biochemical and immunological tests were collected and routinely processed using the techniques performed by the general laboratory of our hospital. Definitions of variables used in this paper are shown in the Appendix. Disease activity and cumulated organ damage were measured by using the SLE Disease Activity Index (SLEDAI) SELENA modification (8) and SDI (1). Arterial stiffness was evaluated by measuring PWV with an automatic device (Complior® Analyse, from ALAM-MEDICAL, Vincennes, France) as we previously described (9).

Statistical analysis

Data were presented as medians (interquartile range, [IQR]) and as percentages. Differences between continuous variables were tested for significance using the Mann-Whitney or Student's *t*-test as appropriate. Categorical data was analysed with Fisher's exact test and odds ratios (OR) and 95% confidence intervals (CI) were calculated. Women with SLE were categorised as with presence (SDI≥1) or absence (SDI=0) of organ damage over time. A linear regression analysis was used to determine the relationship between SDI and PWV after adjustment for appropriate confounders. A multivariate logistic analysis was used to determine which explanatory variables were independently associated with organ damage. A value of $p<0.05$ was defined as statistically significant. Data were analysed using SPSS software for Windows (15.0. SPSS Inc., Chicago, USA).

Results

Finally, 88 women with SLE and 102

sex- and age-matched controls were studied. The main differences between both groups are summarised in Table I. The median duration of SLE was 9 (6–16) years and the median age at diagnosis was 24 (18–33) years. Most of the patients had a stable disease with a median (IQR) SLEDAI score of 2 (0-4). The cumulated frequency of lupus nephritis, neurological involvement and antiphospholipid syndrome was 33%, 8% and 11%. Prednisone and hydroxychloroquine were being taken by 52% and 92% of patients. The median daily prednisone dose was 2.5 (0–5) mg/day and the median cumulated prednisone dose during the last year was 0.6 (0–1.8) g. Immunosuppressants were used concurrently in 34% of patients.

PWV was significantly higher in patients with respect to controls and in patients with damage with respect to those without damage. In addition, patients with increased PWV (see Appendix) were more likely to have organ damage (SDI ≥1) than those with normal PWV (67% *vs*. 36%, p=0.023) (Fig. 1). Finally, they were more likely to have neuropsychiatric damage (17% *vs*. 2%, OR:10 (95%CI 1.2–89)) and tended to present more premature gonadal failure (14% *vs*. 4%, p=0.087).

Patients with damage were older and had been diagnosed later. Also, they were more likely to be obese (20% *vs*. 2%, OR:17 (95%CI 2–188) and have antiphospholipid syndrome (26% *vs*. 7%, OR:4.6 (95%CI 1.2–18). No differences were found in disease activity (SLEDAI) and other SLE-related factors, cardiometabolic parameters and therapies (Table II).

A multivariate logistic analysis was used to determine which explanatory variables were independently associated with COD. The independent variables included in the analysis were those that reached statistical significance in the bivariate analysis (Table II, listed in the Table III). Of them, PWV and obesity emerged as factors independently associated with organ damage (Table III). Both variables accounted for ~20% of its variance (adjusted $R^2 = 0.187$). Finally, PWV and SDI independently correlated after adjustment for age, disease duration, SBP, BMI, eGFR, accumulat-

Table I. Characteristics of participants.

	SLE women n=88	Controls n=102	$p^{\dagger}$
Age, years	35 (29-47)	37 (29-47)	0.74
Secondary education, n (%)	52 (59)	70 (69)	0.50
Obesity, n (%)	5 (6)	9 (9)	0.58
Systolic blood pressure, mmHg	117 (109-126)	115 (108-120)	0.13
Diastolic blood pressure, mmHg	73 (67–80)	72 (67-77)	0.19
Hypertension, n (%)	31 (35)	12 (12)	<0.001
HOMA-IR	1.6 (1.1-2.2)	1.2 (0.9-1.7)	0.012
Metabolic syndrome, n (%)	10 (11)	4 (4)	0.053
Low density lipoprotein, mg/dl	100 (84-115)	110 (92-132)	0.001
High density lipoprotein, mg/dl	58 (47-67)	67 (56-74)	<0.001
Triglycerides, mg/dl	82 (58-106)	61 (46-91)	0.007
eGFR, ml/min/1.73m^2	92 (81-106)	93 (81-103)	0.95
Homocysteine, µmol/l	11 (9-14)	8 (7-10)	<0.001
C-reactive protein, mg/dl	0.1 (0.1-0.3)	0.1 (0.1-0.2)	0.040
ESR, mm/h	16 (8-35)	13 (7-18)	<0.001
Pulse wave velocity, m/s	7.5 (6.8-8.2)	7.1 (6.4-8.7)	0.009
Statins, n (%)	15 (17)	3 (3)	0.001
Antihypertensives, n (%)	26 (30)	6 (6)	<0.001

SLE: systemic lupus erythematosus; HOMA-IR: homeostasis model of assessment – insulin resistance; eGFR: estimated glomerular filtration rate: ESR: erythrocyte sedimentation rate.
†By Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

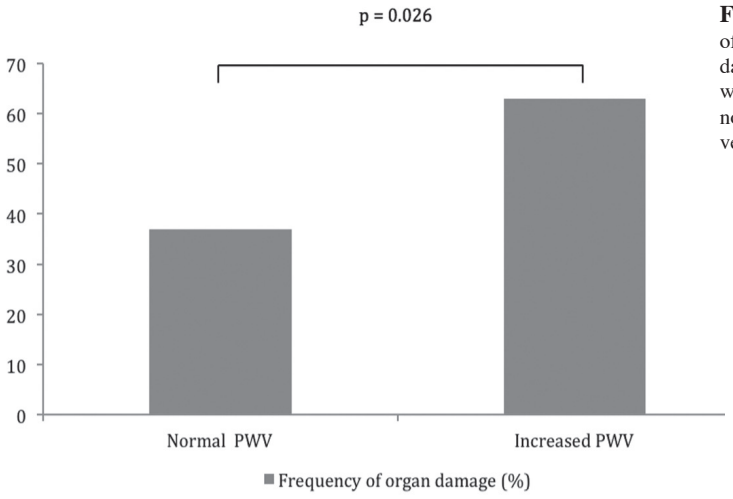

Fig. 1. Frequency of cumulated organ damage in patients with increased or normal pulse wave velocity (PWV).

Appendix: Definitions

1. Hypertension: systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure >90 mmHg or use of medications specifically to treat hypertension at the time of the study.
2. Obesity: body mass index (BMI) >30 kg/m^2.
3. The estimated glomerular filtration rate (eGFR) was automatically calculated using the Modification of Diet in Renal Disease (MDRD)-7 equation (http:// www.semergencantabria.org/calc/cacalc.htm).
4. Chronic kidney disease: An eGFR <60 ml/min/1.73 m^2 for three months
5. Menopausal status: >1 year since last menstrual period.
6. The homeostasis model assessment-insulin resistance (HOMA-IR) was calculated using the formula (HOMA-IR = glucose (mmol/l) x insulin (µU/l / 22.5).
7. Metabolic syndrome (MetS): to have ≥3 of the following criteria: waist ≥88 cm; fasting glucose ≥110 mg/dl; triglycerides ≥150 mg/dl; high density lipoprotein <50 mg/dl; BP: ≥130 mmHg and/or ≥85 mmHg or be on antihypertensive therapy.
8. Increased and normal PWV: PWV above and below the cut-off corresponding to the 75th percentile of PWV from the control group, *i.e*. 7.73 m/s.

Table II. Characteristics of patients with or without organ damage.

	SDI = 0 n=69	SDI ≥1 n=19	$p^{\dagger}$
Age, years	32 (28-44)	44 (34-52)	0.017
Age at diagnosis, years	22 (17-29)	31 (21-39)	0.025
Disease duration, years	8 (6-15)	14 (5-17)	0.32
SLEDAI	2 (0-4)	2 (0-3)	0.35
Antiphospholipid syndrome, n (%)	5 (7)	5 (26)	0.035
Lupus nephritis, n (%)	24 (35)	5 (26)	0.59
Systolic blood pressure, mmHg	117 (108-126)	118 (111-132)	0.41
Diastolic blood pressure, mmHg	72 (67-80)	74 (66-81)	0.39
Hypertension, n (%)	24 (35)	7 (37)	1.0
Obesity, n (%)	1 (1)	4 (21)	0.006
Metabolic syndrome, n (%)	6 (9)	4 (21)	0.13
eGFR, ml/min/1.73m^2	93 (80-107)	88 (82-104)	0.84
Homocysteine, µmol/l	10 (9-13)	12 (8-15)	0.37
HOMA-IR	1.6 (1.1-2.1)	1.7 (1.0-2.9)	0.72
C-reactive protein, mg/dl	0.1 (0.1-0.3)	0.1 (0.1-0.4)	0.98
ESR, mm/h	14 (8-33)	24 (11-36)	0.15
Pulse wave velocity, m/s	7.4 (6.7-8.1)	8.0 (7.4-8.7)	0.007
Prednisone use, n (%)	35 (51)	11 (58)	0.58
Prednisone dose, mg/day	2.5 (0-5)	2.5 (0-5.0)	0.95
Hydroxychloriquine use, n (%)	65 (94)	16 (84)	0.15

SDI: SLICC/ACR Damage Index; SLEDAI: SLE Disease Activity Index; eGFR: estimated glomerular filtration rate; HOMA-IR: homeostasis model of assessment – insulin resistance; ESR: erythrocyte sedimentation rate.
†By Mann-Whitney test for continuous variables and Chi-square for categorical variables.

Table II. Characteristics of patients with or without organ damage.

	Beta	95% confidence interval	*p*
Obesity	0.301	0.177 – 0.870	0.003
Pulse wave velocity	0.282	0.030 – 0.174	0.006

R^2 corrected value: 0.187.
Variables included in the analysis: age, age at diagnosis, obesity, pulse wave velocity, antiphospholipid syndrome.

ed prednisone dose and homocysteine levels (r=0.283, *p*=0.011).

Discussion

To the best of our knowledge, we have documented for the first time that cumulated organ damage and arterial stiffness are independently associated in SLE women with normal renal function and without renal damage, defined according to the specific item in the renal domain of SDI (1).

Few studies had previously reported an association between organ damage and arterial stiffness in patients with SLE (5, 6). The mechanisms that link both conditions are poorly known. Some may consider that this association may be fundamentally due to renal involvement since renal disease has been closely linked to arterial stiffness in the general population (10). Thus, renal dysfunction has been shown to increase arterial stiffness via several mechanisms, including vascular calcification, endothelial dysfunction, inflammation, oxidative stress, and the overproduction of uric acid. Conversely, arterial stiffness causes microvascular damage, especially in the kidney. Therefore, arterial stiffness and renal dysfunction might have a bidirectional cause-effect relationship (11). In line with this, several studies have reported that a history of significant proteinuria or persistent elevated serum creatinine is associated with subclinical atherosclerosis in SLE (12). However, the fact that arterial stiffness and cumulated organ damage are independently associated in SLE women with normal renal function and without renal damage suggests that other domains of SDI can also contribute to an increase in arterial stiffness in these patients. Furthermore, in our study, premature gonadal failure and neuropsychiatric were the most prevalent scored domains in patients with organ damage (36% and 21%, respectively). SLE women with increased PWV compared with those with normal PWV were also more likely to have neuropsychiatric damage and tended to have more premature gonadal failure. Early menopause may reflect higher SLE activity. In the results from the LUMINA cohort, disease activity and cyclophosphamide use emerged as predictors of premature gonadal failure (13). In turn, cyclophosphamide use is associated with a more aggressive disease, higher systemic inflammation and the use of higher doses of corticosteroids, all of them related to increased atherosclerosis in SLE. Neuropsychiatric involvement was also significantly associated with atherosclerotic vascular events in the Toronto inception lupus cohort (14).

Finally, in agreement with others (15), obesity was found to be independently associated with organ damage. Possible mechanisms for this link include hypertension, diabetes, cardiovascular events, thrombosis, systemic inflammation and cognitive impairment, among others.

Several limitations should be considered. Since our study is cross-sectional and both PWV and SDI are dynamic factors that increase throughout the disease, we cannot assert whether a single determination is representative of what happens during the course of the disease or whether this association varies over time. However, PWV and SDI remained independently associated after adjustment for SLE duration, suggesting that this association may persist over time. Furthermore, as a result of the relatively small size sample, this study could not have had enough power to identify other independent associations. Finally, we cannot establish directionality or a relationship of causality between PWV and organ damage. However, as noted above, in a prospective study, cardiovascular damage was associated with the SDI score at the moment of inclusion in the survey

a mean of 6.6 years before (4), suggesting that organ damage may precede the development of atherosclerosis.

In summary, this is the first time that organ damage has been independently associated with PWV, a surrogate marker of subclinical atherosclerosis, in SLE women without renal involvement. Future prospective trials should determine whether organ damage contributes to the development of CVD in these patients and whether its prevention leads to a decrease in atherosclerotic cardiovascular events.

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