Metabolic Syndrome Is Associated with Increased Arterial Stiffness and Biomarkers of Subclinical Atherosclerosis in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Aortic pulse wave velocity (PWV) is an independent predictor of risk for atherosclerotic cardiovascular disease. Metabolic syndrome (MetS) is more prevalent in patients with systemic lupus erythematosus (SLE) compared with matched healthy subjects. Aortic PWV is increased in MetS. The purpose of this cross-sectional study was to determine the association between MetS and aortic PWV and other surrogate biomarkers of subclinical atherosclerosis in SLE.

Methods. One hundred twenty-eight patients with SLE were studied. We established the presence of MetS according to the National Cholesterol Education Program Adult Treatment Panel III definition and we measured PWV, glucose, insulin, glycosylated hemoglobin (HbA_{1c}), insulin sensitivity (HOMA index), lipid levels, uric acid, homocysteine, fibrinogen, D-dimer, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin 6 (IL-6), IL-8, IL-10, C3, C4, autoantibodies, SLE Disease Activity Index (SLEDAI), and Systemic Lupus International Collaborating Clinics/ACR Damage Index. Duration of SLE and treatment was also recorded. Multivariate logistic regression analysis was used to identify independent determinants of increased PWV.

Results. SLE patients with MetS had higher aortic PWV (9.8 ± 2.4 vs 8.5 ± 1.7 m/s; p = 0.002) and increased biomarkers of subclinical atherosclerosis such as CRP, IL-6, C3, uric acid, homocysteine, fibrinogen and D-dimer, compared to those without MetS. HOMA index and insulin and HbA_{1c} levels were also higher in this group. No differences were found in variables related to lupus activity (ESR, C4, SLEDAI, IL-8, IL-10, and treatment for SLE). In the multivariate model, increased PWV was associated with age, male sex, MetS, duration of SLE, and CRP.

Conclusion. MetS may contribute to the development of accelerated atherosclerosis in SLE. (J Rheumatol First Release Sept 1 2009; doi:10.3899/jrheum.081253)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS METABOLIC SYNDROME
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Although the exact mechanisms that lead to the development of atherosclerotic cardiovascular disease (ASCVD) in patients with systemic lupus erythematosus (SLE) are not fully established, traditional and nontraditional cardiovascular risk factors appear to be implicated[1]. Metabolic syndrome (MetS) is defined as a clustering of CVD risk factors, characterized by central obesity, glucose intolerance, hypertension (HTN), dyslipidemia, insulin resistance (IR), and a systemic proinflammatory and procoagulating state[2]. It is increasingly recognized as an independent predictor of cardiovascular morbidity and mortality[3], particularly in women[4]. A relatively high prevalence of MetS has been observed in patients with SLE[5-7]. We found a prevalence 3.8 times higher in SLE patients aged ≤ 40 years in comparison with a control group matched for age, sex, and education level[7]. Moreover, the frequency of ASCVD in the SLE group with MetS was 2.2 times higher than that in the SLE group without MetS, suggesting that MetS by itself may contribute significantly to the development of ASCVD in these patients[7].

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Recently, several longitudinal studies directly demonstrated that aortic stiffness, measured using carotid-femoral pulse wave velocity (PWV), is an independent predictor of all-cause and cardiovascular mortality, coronary events, and stroke[8]. Increased vascular stiffness has been found in middle-aged women[9,10], adolescents, and young adults with SLE[11], and it has been suggested that this condition may be a factor contributing to the increased cardiovascular risk observed in these patients.

Although MetS has been associated with increased arterial stiffness among the general population[12,13] and in several patient groups[14,15], the influence of MetS on arterial stiffness in SLE has not been well defined. We conducted a cross-sectional study involving a cohort of SLE patients to explore the link between MetS and PWV and other surrogate biomarkers of subclinical atherosclerosis.

MATERIALS AND METHODS

Participants. One hundred twenty-eight patients with SLE that fulfilled ≥ 4 of the American College of Rheumatology 1997 revised criteria[16] were recruited from the Autoimmune Diseases Unit of our hospital. All participants were White. We excluded SLE patients who had not been monitored for at least 1 year in our unit and patients with a suspected active infection or other disease involving systemic inflammation, except SLE, at the time of inclusion. Patients with ASCVD were also excluded. All participants gave informed consent to participate in this study, which was approved by the local ethics committee.

Protocol and clinical assessment. This was a cross-sectional study conducted over a 4 month period. Patients attending a scheduled visit over the period of the study were assessed for traditional CV risk factors, demographic and education data, comorbidities, and current medications. Other demographic and clinical data were obtained from the medical records in a computer database. Clinical definitions are summarized in the Appendix. Patients were defined as having MetS according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition[19] (Appendix). Disease activity and accumulated organ damage were measured with the SLE Disease Activity Index (SLEDAI)[20] and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)[21], respectively.

Laboratory assessment and assessment of IR. Fasting blood samples for biochemical and immunological tests were collected the day after the scheduled visit and processed routinely the same day, using techniques as described[7]. Other measures studied were glycosylated hemoglobin (HbA_{1c}; by high performance liquid chromatography, HA-8160, Menarini Diagnostics, Florence, Italy); fibrinogen (von Clauss assay); D-dimer (ELISA, Dimertest, Agen Biomedical, Brisbane, Australia); homocysteine (AxSYM Homocysteine; Abbott Laboratories, Abbott Park, IL, USA), and plasma insulin (BioRad, Marne-la-Coquette, France).

HOMA index for IR was calculated according to the formula in the HOMA model[22]. Arbitrarily, SLE patients with a HOMA index value that exceeded the 75th percentile of patients included in the study (≥ 2.51) were classified as having increased IR.

Cytokine measurements. Plasma and serum were separated by centrifugation and stored at –70°C. IL-6 serum concentration was measured by immunoradiometric assay using commercial kits (BioSource Europe, Nivelles, Belgium). Similarly, plasma IL-8 and IL-10 levels were estimated using commercial ELISA kits (R&D Systems, Minneapolis, MN, USA) following the manufacturer's instructions. The intra- and interassay coefficients of variation for biomarkers were IL-6, 4.3% and 2.3%; IL-8, 6.3% and 8%; IL-10, 3.2% and 4.3%, respectively.

Pulse wave velocity measurement. Arterial stiffness was evaluated by measuring carotid-femoral (aortic) PWV using an automatic device (Complior; Colson, Createch Industrie, France) by a single blinded researcher (JAVH) unaware of patients' MetS status. Two pressure waves were recorded transcutaneously at the right common carotid artery and over the right femoral artery. PWV was established as the foot-to-foot velocity. Pulse transit time was established as the average of 10 consecutive beats. The distance travelled by the pulse wave was measured over the body surface as the distance between the 2 recording sites. Aortic PWV was automatically calculated as the ratio of distance to transit time [PWV = D/t(m/s)]. The validation of this automatic method and its reproducibility has been well established[23]. We arbitrarily defined an abnormally increased PWV as the value exceeding the 75th percentile of SLE patients included in the study (≥ 9.67 m/s).

Statistical analysis. The data are presented as the median (range) for continuous variables and percentage for categorical variables. Differences between continuous variables were tested for significance using the Mann-Whitney test. Categorical data was analyzed using Pearson's chi-square test. Categories of HOMA index were defined as presence of IR (HOMA index ≥ 2.51) or absence of IR (HOMA index < 2.51). PWV was categorized as increased arterial stiffness (PWV ≥ 9.67 m/s) or normal arterial stiffness (PWV < 9.67 m/s). A multivariate logistic regression analysis was used to identify independent determinants of increased PWV (dependent variable) in SLE patients. The independent determinants tested were age, sex, HTN, MetS, C-reactive protein (CRP) level, uric acid level, hydroxychloroquine (HCQ) use, HOMA index, and SDI. All analyses used a 5% two-sided significant level. Statistical analyses were carried out using SPSS software for Windows (version 14.0; SPSS Inc., Chicago, IL, USA).

RESULTS

One hundred twenty eight patients with SLE (88% women; median age 40 yrs, range 16–78 yrs) were studied. Twenty-six (20%) were diagnosed as having MetS, a frequency similar to that previously found in our SLE cohort[7]. The median disease duration in this SLE cohort was 11 years (range 1–50), median age at disease onset was 28 years (range 11–76), and the median education level was 8.5 years (range 0–17). Forty-six patients (36%) had renal involvement and 19 (15%) experienced neurological manifestations. The median SLEDAI value for all patients was 4 (range 0–18), indicating that most patients had inactive or moderately active disease status. The median SDI was 1 (range 0–8). At the time of recruitment 88 (69%) patients took prednisone, 95 (74%) received hydroxychloroquine (HCQ), and 43 (33%) were receiving immunosuppressive therapy (1, periodic treatment with intravenous cyclophosphamide because of active lupus nephritis; 7, mycophenolate mofetil, median 750 mg/day; 10, methotrexate therapy, median 10 mg/wk; and 25, azathioprine, median 100 mg/day). In order to establish the presence of MetS in this series, we established 2 categories — i.e., with or without immunosuppressive therapy.

Demographic and metabolic differences between SLE patients with and without MetS. The main differences between SLE patients with and those without MetS are shown in Table 1. To summarize, SLE patients with MetS were older, they had a lower level of education, and the age at onset of SLE was higher. As expected, they had higher blood pressure and body mass index, as well as higher levels

Table 1. Demographic, clinical, and metabolic characteristics of SLE patients with and without metabolic syndrome. Values are median (range) unless stated otherwise.

Characteristic	Metabolic Syndrome		p†
	Yes, n = 26	No, n = 102	
Age, yrs	52 (21–78)	39 (16–73)	0.001
Female, %	85	88	NS
Duration of SLE, yrs	12 (1–38)	11 (0–50)	NS
Age of SLE onset, yrs	32 (17–76)	28 (11–58)	0.006
Education level, yrs	8 (0–15)	11 (0–17)	0.001
Body mass index, kg/m^2	32 (22–51)	24 (18–41)	< 0.001
Waist circumference, cm	104 (83–123)	82 (64–116)	< 0.001
Systolic blood pressure, mm Hg	134 (95–164)	116 (80–160)	< 0.001
Diastolic blood pressure, mm Hg	86 (60–100)	74 (51–103)	0.001
Pulse pressure, mm Hg	50 (26–96)	42 (20–80)	0.001
Fasting glucose, mg/dl	88 (70–165)	81 (58–127)	< 0.001
Glycosylated hemoglobin, %	5.8 (5.0–9.0)	5.5 (4.0–7.0)	0.006
Triglycerides, mg/dl	162 (77–287)	88 (36–201)	< 0.001
Total cholesterol, mg/dl	202 (122–285)	178 (114–283)	NS
HDL cholesterol, mg/dl	46 (19–96)	61 (36–108)	< 0.001
LDL cholesterol, mg/dl	127 (67–202)	101 (44–170)	0.006
Hemoglobin, mg/dl	13 (8–17)	14 (10–17)	NS
White cell count, 10^9/l	5.6 (2.2–14.1)	5.4 (2.5–13.1)	NS
Insulin, mU/l	12.5 (3–30)	6.9 (2–29)	< 0.001
HOMA index	2.5 (1–12)	1.4 (0–6)	< 0.001
Insulin resistance, %*	48	19	0.002
Microalbuminuria, mg/l	125 (5–326)	115 (18–256)	NS
Other traditional risk factors, %			
Hypertension	85	51	0.002
Dyslipidemia	96	69	0.009
Diabetes mellitus	19	1	0.001
Obesity	81	12	< 0.001
Current smokers	31	48	NS
Sedentary lifestyle	46	42	NS
Family history of premature CVD	15	17	NS
Alcohol consumption	15	20	NS
Postmenopausal status	41	20	NS

* HOMA index ≥ 2.51. † Pearson chi-square test for categorical variables and Mann-Whitney test for continuous variables. NS: nonsignificant; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA: homeostasis model assessment; CVD: cardiovascular disease.

of fasting glucose, HbA_{1c}, insulin, HOMA index, and triglycerides, and decreased levels of high-density lipoprotein. Low-density lipoprotein levels were also found to be higher in these patients. Consequently, SLE patients with MetS were more likely to suffer from obesity (OR 32, 95% CI 10–99, p < 0.001), HTN (OR 5.3, 95% CI 1.7–16.4, p = 0.002), dyslipidemia (OR 11.4, 95% CI 1.5–88, p = 0.009), diabetes mellitus (OR 24, 95% CI 2.7–99, p = 0.001), and increased IR (OR 4.1, 95% CI 1.6–10.3, p = 0.002).

PWV, SLE-related factors, and biomarkers. SLE patients with and without MetS differed significantly with regard to arterial stiffness, given that average aortic PWV was significantly higher in the MetS group compared to the non-MetS group (p = 0.002). Interestingly, inflammatory biomarkers such as CRP and IL-6 and other markers associated with ASCVD including C3 complement, uric acid, homocysteine levels, fibrinogen, and D-dimer concentrations were also significantly higher among SLE patients with MetS (Table 2). In contrast, no differences in ESR, IL-8, and IL-10 were found (Table 2). Hemoglobin levels and white blood cell counts were also similar in both groups, as well as the autoantibody pattern (anti-nDNA, Ro, La, RNP, and antiphospholipid antibodies; data not shown).

SLE patients with and without MetS undergoing treatment. More SLE patients with MetS took antihypertensive agents than those without MetS (p = 0.047). The rest of the treatments administered were similar in both groups (Table 2). The percentage of immunosuppressive agents taken in each group (with and without MetS, respectively) was as follows: azathioprine 4% versus 6%; cyclophosphamide 1% versus 1%; methrotexate 8% versus 8%; mycophenolate mofetil 18% versus 20%; and cyclosporine 0% versus 2%.

Differences in demographic, metabolic, and SLE-related factors between SLE patients with normal PWV and those with increased PWV. MetS was closely associated with increased PWV (50% vs 18% normal; OR 4.36, 95% CI

Table 2. Pulse wave velocity, inflammatory, prothrombotic and subclinical arteriosclerosis biomarkers, and treatment in SLE patients with and without metabolic syndrome. Values are median (range) unless stated otherwise.

Characteristic	Metabolic Syndrome Yes, n = 26	No, n = 102	p†
Pulse wave velocity, m/s	9.7 (6–18)	8.4 (3–13)	0.002
C reactive protein, mg/dl	0.2 (0–2.0)	0.1 (0–7.0)	0.010
Erythrocyte sedimentation rate, mm/h	26 (6–89)	23 (1–121)	NS
Interleukin 6, pg/ml	13.4 (1–191)	1.7 (0–114)	0.050
Interleukin 8, pg/ml	2.0 (1–54)	2.0 (0–106)	NS
Interleukin 10, pg/ml	13.8 (3–223)	9.9 (2–331)	NS
C3, mg/dl	115 (48–152)	96 (33–162)	0.008
C4, mg/dl	23.5 (1–50)	19.9 (1–51)	NS
Uric acid, mg/dl	5.6 (2.0–8.0)	4.3 (2.0–9.0)	0.002
Homocysteine, μmol/l	14.4 (10–39)	12.9 (7–25)	0.026
Fibrinogen, mg/dl	367 (274–438)	317 (208–851)	0.023
D-dimer, μg/ml	0.4 (0–2.0)	0.3 (0–3.0)	0.009
SDI	1.0 (0–8)	1.0 (0–7)	NS
SLEDAI	4.0 (0–18)	4.0 (0–18)	NS
Antihypertensive agents, %	69	45	0.047
Statins, %	23	24	NS
Hypoglycemic agents, %	4	0	NS
Nonsteroidal antiinflammatory drugs, %	65	52	NS
Current prednisone dose, mg/day	4.4 (0–10)	3.8 (0–20)	NS
Prednisone, %	58	71	NS
Hydroxychloroquine, %	65	76	NS
Immunosuppressant agents, %	28	37	NS

† Pearson chi-square test for categorical variables and Mann-Whitney test for continuous variables. NS: nonsignificant; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity index.

1.7–10.9, p < 0.001; Figure 1), and as expected MetS was associated with increased IR (48% vs 19% normal; OR 4.05, 95% CI 1.5–10.4, p = 0.002). The association between increased IR and increased PWV was no longer significant (p = 0.5) and the HOMA index was similar between patients with normal and those with increased PWV (Table 3). The main differences between patients with increased and normal PWV are shown in Table 3. To summarize, no differences were found in the variables related to lupus activity; however, some factors linked to ASCVD and atherosclerosis burden were more significant in the group with increased vascular stiffness. When evaluating treatment, it is notable that in the univariate analysis, the probability of use of HCQ tended to be higher in the SLE group with normal PWV, but this did not reach statistical significance (p = 0.056). Finally, patients with increased vascular stiffness had a significantly higher SDI.

In a multivariate analysis, age, male sex, presence of MetS, duration of SLE, and CRP levels were independently associated with an increased PWV (Table 4). This model correctly classified 71% of patients, with a cutoff value of 0.5.

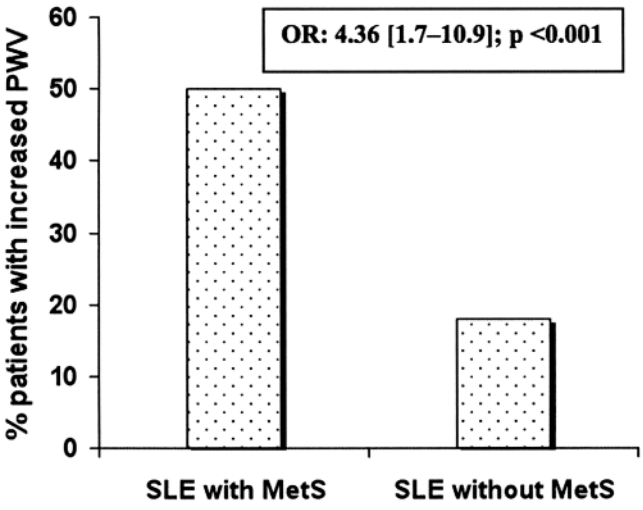

Figure 1. Percentage of SLE patients with increased pulse wave velocity (PWV) according to metabolic syndrome (MetS) status.

DISCUSSION

The main finding of our study was a close link between the presence of MetS and increased aortic stiffness (OR 4.36, p < 0.001) and CRP levels in patients with SLE. These results support the hypothesis that MetS may contribute to the development of atherosclerosis in SLE patients, which could in part explain the excess of ASCVD observed in this population.

MetS occurs more frequently in SLE patients than in healthy subjects with similar characteristics[5-7]. Several stud-

Table 3. Characteristics of SLE patients with normal or increased pulse wave velocity (PWV). Values are median (range) unless stated otherwise.

Characteristic	Increased PWV*, n = 32	Normal PWV*, n = 96	p†
Age, yrs	56.5 (18–78)	38 (16–69)	< 0.0001
Female sex, %	75	88	0.026
Duration of SLE, yrs	16 (2–50)	10 (1–38)	0.001
Age of SLE onset, yrs	37 (11–76)	28 (12–53)	< 0.0001
Education level, yrs	8 (0–15)	11 (0–17)	0.012
Waist circumference, cm	93 (67–123)	84 (64–121)	0.005
Systolic blood pressure, mm Hg	125 (97–164)	116 (80–160)	< 0.0001
Diastolic blood pressure, mm Hg	78 (55–100)	75 (51–103)	0.04
Pulse pressure, mm Hg	50 (30–96)	41 (20–80)	< 0.0001
Fasting glucose, mg/dl	86 (63–185)	81 (58–96)	0.001
Triglycerides, mg/dl	105 (50–287)	95 (46–268)	0.035
Total cholesterol, mg/dl	196 (130–285)	182 (114–283)	NS
HDL cholesterol, mg/dl	52.5 (32–96)	58 (19–108)	NS
LDL cholesterol, mg/dl	119 (52–202)	105 (54–170)	NS
Glycosylated hemoglobin, mg/dl	5.7 (4.9–9.0)	5.5 (3.9–7.2)	0.008
Insulin, mU/l	7.8 (2.0–29.9)	8.5 (2.0–28.2)	NS
HOMA index	1.7 (0.3–12.1)	1.8 (0.4–26.2)	NS
C-reactive protein, mg/dl	0.45 (0.1–7.4)	0.15 (0.1–3.4)	0.046
Erythrocyte sedimentation rate, mm/h	25 (1–121)	23 (1–105)	NS
Interleukin 6, pg/ml	4.1 (1.5–129)	2.6 (1.2–162)	NS
Interleukin 8, pg/ml	2.0 (0.6–56)	2.0 (0.3–106)	NS
Interleukin 10, pg/ml	12.8 (5–289)	11.9 (2–257)	NS
C3, mg/dl	109 (62–162)	97 (33–159)	NS
Uric acid, mg/dl	5.5 (1.8–9.3)	4.3 (2.5–9.1)	0.004
Homocysteine, μmol/l	14 (11–23)	12.7 (7–39)	0.034
Fibrinogen, mg/dl	375 (541–851)	320 (208–743)	0.018
D-dimer, μg/dl	0.4 (0.2–2.3)	0.3 (0.1–2.9)	NS
SDI	2.0 (0–8)	1.0 (0–5)	0.020
SLEDAI	4.0 (0–18)	4.0 (0–17)	NS
Prednisone, %	66	72	NS
Current prednisone dose, mg/day	3.6 (0–15)	4.2 (0–15)	NS
Hydroxychloroquine, %	59	78	0.056

* Increased PWV: ≥ 75th percentile (≥ 9.67 m/s). Normal PWV: < 75th percentile (< 9.67 m/s). † Pearson chi-square test for categorical variables and Mann-Whitney test for continuous variables. NS: nonsignificant; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA: homeostasis model assessment; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity index.

Table 4. Variables associated with increased pulse wave velocity in patients with SLE, using logistic regression.

Explanatory Variable	ß Coefficient	OR (95% CI)	p
Age	0.05	1.1 (1.05–1.10)	0.010
Male sex	1.49	4.43 (1.14–17.9)	0.030
Metabolic syndrome	1.07	2.93 (1.05–8.93)	0.050
SLE duration	0.05	1.05 (1.0–1.63)	0.050
C-reactive protein	0.80	2.22 (1.03–5.46)	0.040

ies have consistently shown an association between MetS and arterial stiffness[13], which has been proven to be a marker of early vascular changes that may lead to major vascular disease[8]. Increased aortic PWV has been observed in SLE patients and even in adolescents[11]. Selzer, *et al* found that higher aortic stiffness in women with SLE was associated with a combination of SLE-related and CV risk factors[24]. Bjarnegrad, *et al* found that aortic PWV was positively associated with CRP and C3 in middle-aged women with SLE[10]. Finally, a link between MetS and carotid artery intima-media thickness has been found in patients with rheumatoid arthritis (RA)[25]. However, the influence of MetS itself on arterial stiffness in SLE patients remains largely unknown. Although initially a positive association between increased

aortic stiffness and MetS in SLE patients was expected, the deleterious effect of MetS on arterial stiffness could equally be completely or partially overshadowed by SLE-related factors, in particular by low-grade systemic inflammation and therapies. In a recent study in which RA was accompanied by increased arterial stiffness, a reduction of systemic inflammation using anti-tumor necrosis factor-α therapies decreased aortic stiffness to a level comparable to that of healthy individuals[26].

SLE and atherosclerosis share some biochemical mediators as a result of the underlying chronic inflammation status in both conditions. CRP and IL-6 have been associated with atherosclerosis burden[24,27], MetS[7,28], arterial stiffness[10,29], and lupus disease activity[30]. In contrast, increased plasma concentrations of IL-8 and IL-10 have been found to correlate mainly with disease activity in SLE patients[30,31]. Thus, Asanuma, *et al* found no link between IL-8 and coronary artery calcification[27]. In our study, SLE patients with MetS had significantly higher levels of CRP and IL-6 compared to those without MetS. These data might be interpreted as the result of increased systemic inflammation due to major lupus activity. However, all measures associated with lupus activity, including SLEDAI, ESR, IL-8, IL-10, hemoglobin levels, white blood cell count, prednisone dose, and use of immunosuppressive agents, were similar in both groups. In contrast, lupus patients with MetS had higher levels of some new markers associated with ASCVD and MetS in SLE patients or in the general population, such as C3[7,9,10], uric acid[7,32], homocysteine levels[33-35], fibrinogen[36-39], and D-dimer concentrations[39,40]. Consequently, it seems reasonable to attribute the excess of CRP and IL-6 levels to major atherosclerosis burden in the MetS group, as it coincides with the increased arterial stiffness observed in these patients. It is worth emphasizing that a recent study showed that IL-6 and CRP levels correlated with arterial stiffness in patients with SLE and RA[28]. On the other hand, MetS was associated with increased PWV in the univariate analysis (OR 4.36, $p < 0.001$; Figure 1) and in the multivariate model (Table 4). Moreover, SLE patients with increased PWV had higher biomarker levels of atherosclerosis such as CRP, uric acid, homocysteine, and fibrinogen. They also had a significantly higher level of HbA_{1c}, recently identified as a biomarker independently associated with MetS[41]. Similarly, the education level of SLE patients with increased aortic stiffness was lower, which has also been linked to a higher prevalence of MetS affecting patients with SLE[7] and the general population[42].

Our results were particularly interesting because, unlike findings from Selzer, *et al*[24] showing that increased aortic PWV was associated with a combination of SLE-related variables and traditional CV risk factors in the logistic regression analysis, we found that arterial stiffness was fundamentally associated with variables unrelated to SLE (age, presence of MetS, sex, and CRP levels), with the exception of the duration of lupus (Table 4). This discrepancy could be due to the differences in the demographic characteristics of patients included in the 2 studies.

Finally, increased PWV was associated with a higher SDI. This finding could be attributed to at least 2 facts: first, patients with increased arterial stiffness were older, and second, the duration of lupus in this group was significantly longer.

Regarding IR, this is thought to be a relevant contributor to the increased CV risk attributed to MetS in the general population. Indeed, IR contributed to the association between MetS and coronary artery calcification in nondiabetic subjects, independent of age, non-MetS risk factors, and CRP[43]. As expected, MetS was found to be associated with increased IR in SLE patients (OR 4.05, $p = 0.002$). However, the association between increased IR and increased PWV was not significant ($p = 0.5$). These results coincide with those obtained by Chung, *et al*[44] in a recent study in which IR was associated with coronary artery calcification in RA, but not in SLE. The reason that increased PWV is associated with MetS, but not with IR, might be that, although closely linked, the 2 concepts are not exactly the same. It is well established that not all patients with MetS defined by the ATP III criteria have IR and not all patients with IR meet the criteria for MetS[45]; therefore, it is likely that patients included in both groups (MetS and IR) were not the same. On the other hand, in the study by Chung, *et al* the major contributing factors to IR in RA were inflammation markers and disease activity[44]. In contrast, in SLE, IR was associated fundamentally with obesity, but not with inflammation markers or lupus activity, except ESR[44]. In accord with these results, increased IR in our SLE patients was closely associated with obesity (OR 3.6, 95% CI 1.5–8.7, $p = 0.003$), CRP, ESR, and IL-6 levels, with SLEDAI scores being similar in patients with and without increased IR (data not shown).

Age could be a potential confounder in this study. The prevalence of MetS increases with age[42]. Yet advancing age, among other factors, is a major contributor to the development of sustained increased arterial stiffness[46]. SLE patients with MetS were significantly older than those without. Similarly, SLE patients with increased PWV were also older compared to those with normal PWV. In the multivariate analysis, age, as well as MetS, was independently associated with aortic stiffness. In the general population cohort, MetS accelerated the age-related progression of arterial stiffness with respect to subjects with 0, 1, or 2 CV risk factors, contributing to the development of premature vascular senescence in these patients[13].

We found that therapies did not influence the results. Only antihypertensive agents were taken more frequently by SLE patients with MetS. Even so, these patients had higher PWV despite the fact that the most powerful method of treatment for reducing arterial stiffness is to vigorously treat

HTN. It is worth noting that in the univariate analysis (but not in the multivariate analysis), non-use of HCQ tended to be associated with an increased PWV (p = 0.056). Selzer, *et al*[9] found a significant association between the non-use of HCQ and increased PWV among premenopausal women. Similar results were also obtained by Tanay, *et al*[47]. Previously, Roman, *et al* found that HCQ treatment was associated with a lower presence of carotid plaque in SLE patients[48]. These findings suggest that HCQ might exert a protective effect on the vessel wall. We previously found that the use of HCQ was inversely associated with the presence of MetS in SLE patients[7]. Although the prevalence of MetS in SLE patients receiving HCQ (65%) was 15% lower than in those who did not take HCQ (76%), this inverse association was not statistically significant in the present study, probably due to the relatively small number of patients.

Some major limitations of our study should be considered. First, we did not include a healthy control group. Second, the design constituted a limitation, although this is common to the majority of studies that investigate underlying mechanisms of accelerated atherosclerosis in SLE. Since atherosclerosis is a slow process that evolves over months or years, a cross-sectional study based on single random measurements of aortic PWV and other inflammatory biomarkers cannot establish a cause-effect relation between MetS and vascular stiffness. For example, this design does not account for key issues such as how long a patient has had MetS. Therefore, prospective studies are needed to determine the exact role of MetS in the development of accelerated atherosclerosis in patients with SLE.

Despite these limitations, the results together suggest a close link between MetS and vascular stiffness in SLE. Moreover, MetS may increase aortic stiffness to a greater extent than IR and SLE activity. This aspect could be relevant in clinical practice, since MetS can be modified with appropriate pharmacological interventions and certain changes to lifestyle, which could prevent or delay the development of accelerated atherosclerosis in these patients. This hypothesis requires confirmation through further interventional studies.

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APPENDIX. Terms used in the text.

Obesity: body mass index ≥ 30 kg/m^2.

Hypertension, systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg, or on antihypertensive therapy at the time of the study[17].

Pulse pressure: difference between SBP and DBP.

Diabetes mellitus: on treatment with oral hypoglycemic agents or insulin, or fasting blood glucose (FBG) > 126 mg/dl at time of assessment[18].

Dyslipemia: total cholesterol ≥ 190 mg/dl or low density lipoprotein ≥ 115 mg/dl, or high density lipoprotein (HDL) ≤ 40 mg/dl in men and ≤ 46 mg/dl in women or triglycerides (TG) ≥ 150 mg/dl, on treatment with hypolipemic drug therapy[19].

Smoking habit: smoker: current smoking; nonsmoker: the remainder of the patients.

Alcohol consumption: nondrinkers: < 10 g ethanol/day; drinkers ≥ 10 g ethanol/day.

Sedentary lifestyle: < 200 minutes/week of moderate intensity physical activity, besides habitual activity.

Family history of atherosclerotic cardiovascular diseases: first-degree relative who had had a myocardial infarction or stroke < 55 years old in men, < 65 years old in women.

Metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III definition): ≥ 3 of the following criteria: (1) waist circumference ≥ 102 cm in men, ≥ 88 cm in women; (2) SBP ≥ 130 mm Hg, or DBP ≥ 85 mm Hg, or use of antihypertensive therapy; (3) FBG ≥ 110 mg/dl; (4) triglycerides ≥ 150 mg/dl; (5) HDL < 40 mg/dl in men, < 50 mg/dl in women.

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