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Factors associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico

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Abstract

The aim of this study was to determine the factors associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico. A total of 204 patients with systemic lupus erythematosus (per the American College of Rheumatology classification criteria) were evaluated. Metabolic syndrome was assessed using the American Heart Association and the National Heart, Lung, and Blood Institute classification. Socioeconomic–demographic parameters, health-related behaviours, clinical manifestations, autoantibodies, pharmacological treatments, disease activity (per the Systemic Lupus Activity Measure—Revised), and damage accrual (per the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index) were determined at study visit. Factors associated with metabolic syndrome were examined by univariable analyses and multivariable logistic regression models. A total of 196 (96.2%) were women. The mean age at study visit was 43.6 ± 13.0 years, and the mean disease duration was 8.7 ± 7.7 years. Seventy-eight patients (38.2%) had metabolic syndrome. In the multivariable analysis, age (odds ratio [OR] = 1.05; 95% confidence interval [CI] 1.02–1.09), government health insurance (OR = 2.06; 95% CI 1.07–4.22), exercise (OR = 0.33; 95% CI 0.14–0.92), thrombocytopenia (OR = 4.19; 95% CI 1.54–11.37), erythrocyte sedimentation rate (OR = 1.64; 95% CI 1.03–2.63), disease activity (OR = 1.14; 95% CI 1.00–1.30), and prednisone >10 mg/day (OR = 3.69; 95% CI 1.22–11.11) were associated with metabolic syndrome. In conclusion, older age, low socioeconomic status, lack of exercise, thrombocytopenia, increased erythrocyte sedimentation rate, higher disease activity, and prednisone >10 mg/day were independently associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico.

Key indexing terms

cardiovascular disease; haematologic changes; systemic lupus erythematosus; Metabolic syndrome; Puerto Rico

Introduction

Metabolic syndrome is characterized by a group of interrelated metabolic risk factors that confer a proinflammatory and a prothrombotic state.¹ These risk factors promote the development of atherosclerotic cardiovascular disease and/or type 2 diabetes mellitus.^{1–3} Metabolic syndrome is manifested by the presence of hypertension, glucose intolerance, dyslipidaemia, and obesity.⁴ The prevalence of metabolic syndrome in the United States ranges from 22 to 36.7%.^{5,6} It increases with age, from 25% in adults older than 20 years to 45% in

adults older than 50 years.^{4,5} The prevalence of metabolic syndrome is increasing in young women.⁷

A number of different classification criteria have been proposed since 1998 to define metabolic syndrome.^{1,8–10} The most recent one was proposed in October 2005 when the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) modified the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria.¹

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease with multi-organ/multi-system involvement, which primarily affects women in their reproductive age.^{11,12} A bimodal mortality pattern is observed in patients with SLE.¹³ Early mortality is more likely to be related to disease itself, whereas late mortality is mainly associated with co-morbidities, coronary artery disease being one of the most common causes of morbidity and mortality at this stage of disease.^{14–18} Regardless of the specific components present, it is important to assess metabolic syndrome in SLE to identify those patients at greater risk for coronary artery disease.¹⁹ However, the prevalence of metabolic syndrome, as well as the factors associated with it, is not well known in patients with lupus. We hypothesize that demographic–socioeconomic parameters, clinical manifestations, serological features, pharmacological treatment, disease activity, and damage accrual are associated with metabolic syndrome in patients with SLE from Puerto Rico.

Patients and methods

Patient population

A cross-sectional study was carried out in 204 patients with SLE. All patients met at least 4 of the 11 American College of Rheumatology (ACR) classification criteria for SLE.²⁰ Patients with SLE were recruited from the lupus clinic of the University of Puerto Rico Medical Sciences Campus in San Juan, Puerto Rico, and from a private rheumatology practice located in San Juan, Puerto Rico. Pregnant women were excluded. All patients with SLE seen between April and July 2006 were enrolled. This study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus Human Research Protection Office.

Before the study visit, patients made routine visits at 3-month intervals. Additional visits were scheduled according to disease activity or complications. At each routine visit, a structured questionnaire was completed for each patient to gather information about demographic parameters, health-related behaviours, clinical manifestations, laboratory tests [complete blood cell count, comprehensive metabolic panel, urine analysis, erythrocyte sedimentation rate (ESR), and lipid panel], pharmacologic treatment, disease activity, and disease damage. For all patients, a lupus autoantibody panel was carried out at the time of SLE diagnosis.

Assessment of metabolic syndrome

The AHA/NHLBI classification was used to determine the presence of metabolic syndrome at study visit.¹ Patients were said to have metabolic syndrome if three or more of the following criteria were present: arterial hypertension (≥ 130 mm Hg systolic blood pressure or ≥ 85 mm Hg diastolic blood pressure or drug treatment for hypertension), increased fasting blood glucose (≥ 100 mg/dL or drug treatment for diabetes), reduced high-density lipoprotein (HDL)-cholesterol (< 40 mg/dL in men, < 50 mg/dL in women or drug treatment for reduced HDL-cholesterol), increased triglycerides (≥ 150 mg/dL or drug treatment for hypertriglyceridaemia), and increased waist circumference (≥ 102 cm in men, ≥ 88 cm in women). Body mass index was also measured at study visit.

Variables

Factors from the demographic–socioeconomic, health-related behaviour, clinical, immunologic, and pharmacologic domains were studied in SLE patients with and without metabolic syndrome. All variables were assessed at study visit except immunologic features, which were determined at diagnosis of SLE.

The following socioeconomic–demographic parameters were examined: age, gender, disease duration (time interval between SLE diagnosis and study visit), and type of health care insurance (private vs government). Health-related behaviours studied included cigarette smoking, alcohol drinking, and exercise. Exercise was defined as regular participation in physical activity as part of a health-enhancing personal fitness plan. Exercise should have been done for at least 3 months before study visit, including at least three sessions per week for 20–60 min per session. Exercise activities included aerobic exercise (i.e., walking, jogging, swimming, cycling) and/or muscle strength training (i.e., weights, tubing, dynamic bands).

The clinical domain included the assessment of SLE manifestations, disease activity, and disease damage. SLE clinical manifestations over time were determined as defined in the ACR classification criteria for SLE.²⁰ Disease activity was determined with the Systemic Lupus Disease Activity Measure–Revised (SLAM-R).^{21,22} Furthermore, disease activity was assessed with ESR. ESR was determined by the Westergren method and was expressed in four categories as defined in the SLAM-R: <25 mm/h, 25–50 mm/h, 51–75 mm/h, and >75 mm/h. Disease damage was assessed using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI).²³

The following serologic parameters were determined at diagnosis: antinuclear, anti-double stranded DNA, anti-Smith, anti-small nuclear ribonucleoparticle, anti-Ro (SSA), and anti-La (SSB) antibodies. In addition, serum complements (C3 and C4) were measured at diagnosis.

The use of (at any time) and the duration of therapy with glucocorticoids (dose ≤ 10 and > 10 mg/day of prednisone or equivalent, and intravenous methylprednisolone pulses), hydroxychloroquine, azathioprine, methotrexate, and cyclophosphamide were determined. Moreover, the use of glucocorticoids at study visit and the cumulative dose of prednisone (or equivalent) were recorded.

Statistical analysis

The Statistical Package of Social Sciences (version 11.0; SPSS, Chicago, Illinois) program was used in univariable and multivariable analyses. Differences between SLE patients with and without metabolic syndrome were analyzed with Chi-square or Fisher's exact tests. Analysis of variance and *t*-test were used to evaluate mean differences. A logistic regression analysis was used to examine the effects of independent factors on the presence or absence of metabolic syndrome. Variables with $P < 0.05$ in the univariable analyses were entered into the multivariable analyses. A P value < 0.05 and a 95% CI that excludes '1' were used to evaluate statistical significance in the latter analyses.

Results

Of the 204 patients with SLE, 196 were women (96.1%). The mean age at study visit was 43.6 ± 13.0 years. Mean disease duration was 8.7 ± 7.7 years. Overall, 38.2% of patients with SLE had metabolic syndrome (≥ 3 or more classification criteria), 19.6% met two classification criteria, 26.0% met one classification criteria, and 16.2% did not meet any criteria.

Table 1 shows the frequency of individual components of the metabolic syndrome classification and body mass index in SLE patients with and without this condition. The most

frequent feature in patients with metabolic syndrome was high waist circumference (91.0%), followed by high blood pressure (85.9%), low HDL-cholesterol (80.8%), hypertriglyceridaemia (56.4%), increased fasting blood glucose, and/or treatment for diabetes mellitus (32.1%). As expected, all individual components of metabolic syndrome were more common in patients with metabolic syndrome than in those without it. Also, body mass index was higher in patients with metabolic syndrome.

Patients with metabolic syndrome were older (46.7 ± 11.7 vs 41.7 ± 13.4 years, $P = 0.006$), had longer disease duration (11.1 ± 8.3 vs 7.2 ± 2.9 years, $P = 0.001$), and more frequently had government health insurance (61.5 vs 43.7%, $P = 0.013$) than those without metabolic syndrome. Patients with metabolic syndrome were less likely to exercise (11.5 vs 26.2%, $P = 0.012$). No differences were found with regard to cigarette smoking and alcohol drinking between these groups. These data are shown in Table 2.

Table 3 shows the frequency of SLE clinical manifestations, serologic features, disease activity, and damage accrual in SLE patients with and without metabolic syndrome. Among clinical manifestations and serologic features, only thrombocytopenia was significantly associated with metabolic syndrome (21.8 vs 7.9%, $P = 0.005$). Patients with metabolic syndrome had higher SLAM-R mean scores (5.7 ± 3.0 vs 4.6 ± 2.6 , $P = 0.020$), ESR ($P = 0.003$), and SDI mean scores (1.1 ± 1.2 vs 0.7 ± 1.2 , $P = 0.023$).

Among the specific components of the SDI, SLE patients with metabolic syndrome had a trend towards more myocardial infarctions than those without metabolic syndrome (2.6 vs 0.0%, $P = 0.071$). However, angina pectoris and cerebral vascular accidents were similar between the groups (data not shown).

As noted in Table 4, the use of prednisone (or equivalent) >10 mg/day (91.0 vs 74.6%, $P = 0.004$) and azathioprine (47.4 vs 33.3%, $P = 0.044$) at any time during the course of the disease was associated with metabolic syndrome. No differences were found for other immunomodulator/immunosuppressive treatments. Prednisone use >10 mg/day at study visit (28.2 vs 11.9% , $P = 0.003$) and the mean cumulative dose of prednisone (27.2 ± 28.5 vs 17.6 ± 28.3 g, $P = 0.019$) were also associated with metabolic syndrome (data not shown). However, the total treatment duration of prednisone (any dose category) and of other immunomodulator/immunosuppressive treatments was not associated with metabolic syndrome (data not shown).

In the multivariable analyses, older age, having the government health insurance, lack of exercise, thrombocytopenia, increased ESR, higher SLAM-R scores, and the use of prednisone >10 mg/day were associated with metabolic syndrome. However, longer disease duration, use of azathioprine, and higher SDI scores did not retain significance in this model. These results are shown in Table 5. An alternate model that included the cumulative prednisone dose, instead of daily doses of >10 mg prednisone, did not show statistical significance for cumulative prednisone dose. All other variables that were significant in the first model retained statistical significance in the alternate model (data not shown).

Discussion

A critical component of lupus treatment is monitoring for early detection of disease flares/manifestations and comorbidities. Metabolic syndrome, a condition that predisposes to atherosclerotic disease, could have an important influence on the morbidity and mortality of patients with SLE and should be routinely examined in lupus patients. Now, we have determined the factors associated with metabolic syndrome in a sample of SLE patients from Puerto Rico and found that older age, low socioeconomic status, lack of exercise, thrombocytopenia, increased ESR, higher disease activity, and the use of prednisone >10 mg/day were independently associated with metabolic syndrome.

We found a higher prevalence of metabolic syndrome in patients with SLE (38.2%) compared with previous studies.^{24,25} For example, Chung, *et al.* found a prevalence of 32.4% using the World Health Organization definition and 29.4% using the NCEP/ATP III classification criteria.²⁴ Furthermore, El Magadmi, *et al.* showed a prevalence of 18% using the latter classification.²⁵ These differences could be attributed in part to the classification criteria we used (AHA/NHLBI), which is more inclusive than the previous ones: including a lower fasting blood glucose threshold (≥ 100 mg/dL) and disease-specific pharmacologic treatments for the definition of its different components.¹

The association of demographic–socioeconomic factors (older age and low socioeconomic status) with metabolic syndrome is consistent with the previous reports.^{4,5,26–29} In the general population, metabolic syndrome is more prevalent in older individuals.^{4,5,26–28} Another important finding of the present study is that patients with metabolic syndrome were more likely to have the government health insurance of Puerto Rico. In Puerto Rico, patients receive their medical care through either the government health system (a managed care system for the medically indigent population) or the private healthcare industry (based on a fee-for-service system). The eligibility for the government health insurance is determined by the annual family income adjusted for the number of individuals in the household. For example, a family of four members with a combined annual income of 8220 US dollars or less is eligible. According to US standards, this income is below poverty level. In agreement with our findings, some studies have reported that a low household income increases the risk of metabolic syndrome.^{28,29} Furthermore, several studies have shown that a lower socioeconomic level is related to higher morbidity and mortality in patients with SLE.^{30–32} Taken together, these findings stress the need for early intervention in vulnerable groups to improve the course and outcome of chronic diseases, including SLE.

The association of metabolic syndrome with thrombocytopenia, higher ESR, and disease activity is noteworthy. However, whether lupus activity is a factor in the development of metabolic syndrome or whether metabolic syndrome is contributing to disease activity is unclear. It is well known that metabolic syndrome confers a pro-inflammatory state characterized by increased circulating adipocytokines such as tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), and acute-phase reactants such as C-reactive protein.^{2,3} However, patients with SLE have higher plasma leptin and TNF- α levels than healthy-controls.³³ Furthermore, TNF- α and IL-6 are associated with increased body mass index, abnormal lipid profile, and disease activity in patients with SLE.^{34–38} Thus, adipocytokines could have an important role in the development of metabolic syndrome and its association with disease activity in lupus patients.

Patients with metabolic syndrome were more likely to use prednisone >10 mg/day during the disease course. This finding could be reflective of their higher disease activity. However, this association could also be related to the fact that glucocorticoids promote hypertriglyceridaemia, increased fatty acid flux to the liver, and insulin resistance throughout the development of visceral fat.³⁹ Therefore, because of deleterious side effects of glucocorticoids, including the possible association with metabolic syndrome, drug therapy should be kept to the lowest effective dose and alternative treatments should be considered early during the course of disease.

Although metabolic syndrome is an important risk factor for coronary artery disease, only a marginal association with myocardial infarction was observed. Moreover, no association with angina pectoris or cerebrovascular accidents was detected. This is probably related to the low number of patients with SLE who had arterial events and the shorter disease duration of our study sample. Longitudinal studies with longer follow-ups would be required to clearly assess the impact of metabolic syndrome on the cardiovascular outcome of lupus patients.

Some differences are noted between our study and others examining metabolic syndrome in SLE. In contrast to the present study, El Magadmi, *et al.* found that SLE women with metabolic syndrome were of the same age as those without metabolic syndrome.²⁵ Moreover, El Magadmi, *et al.* and Chung, *et al.* did not find any association of metabolic syndrome with lupus disease activity or glucocorticoid use.^{24,25} These differences could be related to variability in the study sample (e.g., ethnicity), length of disease duration, and methodology to assess clinical and outcome variables.

The present study has some limitations. First, non-lupus control subjects were not included. However, the prevalence presented here seems to be slightly higher than that reported for Puerto Ricans.⁴⁰ For example, using ATP III criteria, Gómez, *et al.* found that 34.2% of Puerto Rican women have metabolic syndrome.⁴⁰ Second, because this is a cross-sectional study, it is possible that some patients had metabolic syndrome before study visit. Finally, other factors known to be associated with metabolic syndrome, particularly pro-inflammatory cytokines or procoagulant factors such as TNF- α , IL-6, fibrinogen, and PAI-1, were not measured.^{2,3} The presence of these factors could have a role in the emergence of metabolic syndrome in lupus patients.

Despite these limitations, the results presented here have several clinical implications. Metabolic syndrome is an independent risk factor for atherosclerotic disease; thus, it is important to identify patients at risk to develop metabolic syndrome early in the course of SLE. The implementation of strategies such as using alternative immunomodulator/immunosuppressive therapy (other than prednisone) and programs aimed at weight reduction, nutritional counselling and exercise might decrease the risk of metabolic syndrome. However, prospective studies, including interventional trials, are needed to address the role of metabolic syndrome in the course and outcome of lupus.

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Table 1Individual components of metabolic syndrome^a and body mass index in patients with SLE

Feature	Metabolic syndrome (<i>n</i> = 78)	No metabolic syndrome (<i>n</i> = 126)	<i>P</i> value
High blood pressure (%)	67 (85.9)	40 (31.7)	<0.001
Increased fasting blood glucose (%)	25 (32.1)	5 (4.0)	<0.001
Low HDL-cholesterol (%)	63 (80.0)	33 (26.2)	<0.001
Hypertriglyceridemia (%)	44 (56.4)	14 (11.1)	<0.001
High waist circumference (%)	71 (91.0)	42 (33.3)	<0.001
Body mass index, mean (SD)	31.4 (6.5)	25.9 (5.2)	<0.001

^aPer the 2005 American Heart Association and the National Heart, Lung, and Blood Institute classification criteria.

Abbreviations: SLE: systemic lupus erythematosus; HDL: high-density lipoprotein; SD: standard deviation.

Table 2

Demographic–socioeconomic parameters and health-related behaviours in patients with SLE

Features	Metabolic syndrome (<i>n</i> = 78)	No metabolic syndrome (<i>n</i> = 126)	<i>P</i> value
Gender, female (%)	75 (96.2)	121 (96.0)	NS
Age at study visit, mean years (SD)	46.7 (11.7)	41.7 (13.4)	0.006
Disease duration, mean years (SD)	11.1 (8.3)	7.2 (2.9)	0.001
Government health insurance (%)	48 (61.5)	55 (43.7)	0.013
Exercise (%)	9 (11.5)	33 (26.2)	0.012
Cigarette smoking (%)	7 (9.0)	6 (4.8)	NS
Alcohol drinking (%)	0 (0.0)	1 (0.8)	NS

Abbreviations: SD: standard deviation; NS: not significant; SLE: systemic lupus erythematosus.

Table 3
Clinical manifestations, serologic features, disease activity, and damage accrual in patients with SLE

Features	Metabolic syndrome, (n = 78)	No metabolic syndrome, (n = 126)	P value
Clinical manifestations ^a			
Photosensitivity (%)	66 (84.6)	97 (77.0)	NS
Malar rash (%)	61 (78.2)	85 (67.5)	NS
Discoid lupus (%)	14 (17.9)	16 (12.7)	NS
Oral ulcers (%)	31 (39.7)	46 (36.5)	NS
Arthritis (%)	61 (78.2)	90 (71.4)	NS
Serositis (%)	13 (16.7)	21 (16.7)	NS
Pleuritis (%)	12 (15.4)	18 (14.3)	NS
Pericarditis (%)	2 (2.6)	4 (3.2)	NS
Renal disorder (%)	30 (38.5)	35 (27.8)	NS
Proteinuria >0.5 mg/day (%)	28 (35.9)	34 (27.0)	NS
Cellular casts (%)	11 (14.1)	9 (7.1)	NS
Neurological disorder (%)	4 (5.1)	11 (8.7)	NS
Psychosis (%)	1 (1.3)	6 (4.8)	NS
Seizures (%)	4 (5.1)	5 (4.0)	NS
Haemolytic anaemia (%)	6 (7.7)	7 (5.5)	NS
Leukopenia (%)	29 (37.2)	54 (42.9)	NS
Lymphopenia (%)	44 (56.4)	83 (65.9)	NS
Thrombocytopenia (%)	17 (21.8)	10 (7.9)	0.005
Serologic features ^b			
ANA (%)	73 (94.8)	121 (97.6)	NS
Anti-dsDNA (%)	47 (61.8)	66 (52.8)	NS
Anti-Smith (%)	15 (28.3)	22 (21.0)	NS
Anti-Ro (%)	22 (45.8)	35 (32.4)	NS
Anti-La (%)	7 (14.9)	15 (14.2)	NS
Anti-snRNP (%)	14 (28.0)	23 (23.5)	NS
Low C3 (%)	25 (33.3)	41 (33.6)	NS
Low C4 (%)	30 (40.0)	40 (32.5)	NS
SLAM-R score (SD)	5.7 (3.0)	4.6 (2.6)	0.020
Erythrocyte sedimentation rate ^c			
<25 mm/h (%)	38 (48.7)	89 (71.4)	0.003
25–30 mm/h (%)	26 (33.3)	26 (20.6)	
51–75mm/h (%)	7 (9.0)	8 (6.3)	
>75 mm/h (%)	7 (9.0)	2 (1.6)	
SDI score (SD)	1.1 (1.2)	0.7 (1.2)	0.023

^aPer American College of Rheumatology classification criteria for SLE.

^bNot all patients were tested.

^cPer categories of SLAM-R.

Abbreviations: SLE: systemic lupus erythematosus; ANA: antinuclear antibody; dsDNA: double-stranded DNA; snRNP: small nuclear ribonucleoparticle; SLAM-R: Systemic Lupus Disease Activity Measure-Revised; SD: standard deviation; NS, not significant; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 4

Immunosuppressive/immunomodulator treatment at any time in patients with SLE

Drugs	Metabolic syndrome, (<i>n</i> = 78) (%)	No metabolic syndrome, (<i>n</i> = 126) (%)	<i>P</i> value
Prednisone ≤ 10 mg/day	68 (37.2)	99 (78.6)	NS
Prednisone > 10 mg/day	71 (91.0)	94 (74.6)	0.004
Intravenous methylprednisolone pulse	4 (5.1)	10 (7.9)	NS
Hydroxychloroquine	66 (84.6)	113 (89.7)	NS
Azathioprine	37 (47.4)	42 (33.3)	0.044
IV cyclophosphamide	16 (20.5)	17(13.5)	NS
Methotrexate	10 (12.8)	14(11.1)	NS

Abbreviations: SLE: systemic lupus erythematosus; NS: not significant; IV: intravenous.

Table 5

Multivariable analysis of factors associated with metabolic syndrome

Variables	OR	95% CI	P value
Age	1.05	1.02–1.09	0.001
Disease duration	1.03	0.99–1.08	0.186
Government health insurance	2.06	1.07–4.22	0.048
Exercise	0.33	0.14–0.92	0.032
Thrombocytopenia ^a	4.19	1.54–11.37	0.005
SLAM-R	1.14	1.00–1.30	0.047
Erythrocyte sedimentation rate ^b	1.64	1.03–2.63	0.036
SDI	0.99	0.74–1.31	0.928
Prednisone > 10 mg/day	3.69	1.22–11.11	0.021
Azathioprine	1.15	0.52–2.52	0.735

^aPer American College of Rheumatology classification criteria for SLE.^bPer categories of SLAM-R.Abbreviations: SLE: systemic lupus erythematosus; SLAM-R: ^bSystemic Lupus Activity Measurement-Revised; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.