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Metabolic syndrome in Argentinean patients with systemic lupus erythematosus

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The objective was to determine the prevalence of the metabolic syndrome (MS) in patients with systemic lupus erythematosus (SLE) in Argentina, to assess the factors associated to it, and to compare the results with a control group with non-inflammatory disorders. The study included 147 patients with SLE and 119 controls. MS was defined according to criteria by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) Scientific Statement. Demographic characteristics, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) were assessed as well as administration, maximum dose and cumulative dose of prednisone and hydroxychloroquine (HCQ). MS prevalence was 28.6% (CI 95%: 21.4–36.6) in patients with SLE and 16% in controls ($P = 0.0019$). Patients with SLE presented higher arterial hypertension frequency compared with controls (43 vs 25%, $P = 0.007$). When comparing lupus patients with MS ($n = 41$) and without MS ($n = 106$), no significant differences were observed regarding duration of the disease, SLEDAI or cumulative prednisone dose. Cumulative damage was associated independently with MS (OR 1.98; $P = 0.021$), whereas HCQ use was found to be protective (OR 0.13; $P = 0.015$). Patients with lupus presented higher MS prevalence than controls with non-inflammatory disorders, and occurrence of arterial hypertension was also higher. MS was associated with cumulative damage; the use of HCQ showed to be protective against presence of MS. *Lupus* (2009) **18,** 1019–1025.

Key words: metabolic syndrome; systemic lupus erythematosus

Introduction

The metabolic syndrome (MS) defines a group of risk factors involved in developing cardiovascular disease (CVD) and type 2 diabetes.[1–3] This syndrome, which is characterised by obesity, arterial hypertension, hyperglycaemia, insulin resistance, elevation of triglycerides and low high-density lipoprotein (HDL)-cholesterol levels, has been shown during the last decade to be an independent cardiovascular mortality predictor.[4] In the general population, women suffering from MS run a twofold risk to contract severe CVD and die.[5,6] MS prevalence adjusted for age according to the National Cholesterol Education Program (NCEP) ATP III guidelines is 23.7% in the United States, a number that increases with increasing age and in different ethnic groups like Mexican-Americans (31.9%).[4]

MS is closely related to the inflammatory response.[7] It has been observed that proinflammatory cytokines like IL-6 and TNF-α facilitate insulin-resistance[8,9] and that patients with MS present high levels of CRP, IL-1β, IL-1RA, P-selectin, Inter-Cellular Adhesion Molecule 1 (ICAM-1) and leptin.[10,11] However, it has been found that the intensity of treatment with anti-inflammatory and immunosuppressive drugs on these mediators would play a role in the treatment of the metabolic disease and consequently CVD.[12,13]

In patients with systemic lupus erythematosus (SLE), prevalence of premature atheromatosis is

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increased,[14] and this condition is associated with late mortality. Although patients with SLE have a high prevalence of traditional risk factors for atherosclerosis (Framingham risk factors), the rate of vascular events has been found to be more than seven times that attributed to traditional risk factors.[15,16] Furthermore, patients with lupus *per se* present a proatherogenic lipid profile: they have elevated levels of triglycerides and low levels of HDL-cholesterol; hence, they suffer the loss of anti-inflammatory properties of HDL, which is transformed into a proinflammatory agent, and consequently low-density lipoprotein (LDL) oxidation is increased.[17,18]

To detect modifiable and predisposing factors contributing to atherosclerosis, several authors have studied MS in rheumatic inflammatory diseases, mainly SLE and rheumatoid arthritis (RA), with contradictory results.[19–23] To date, there exist few reports on MS in Latin-American patients with lupus.[24–26] Our objective was to determine MS prevalence in Argentinean patients with SLE, compare their outcomes to those from a control group (CG) and analyse the conditions associated with MS, principally established treatments.

Materials and methods

This is a cross-sectional study involving 147 patients with SLE (classified according to ACR criteria[27]) from Argentina. Patients were enrolled consecutively between July 2006 and December 2007. They needed to have been diagnosed at least 6 months before enrolment and they all attended eight Rheumatology Centres in different provinces; all were evaluated and monitored with similar criteria. The CG included 119 patients without inflammatory rheumatic disease (osteoarthrosis, traumatisms, mechanic low back pain and fibromyalgia).

All patients (SLE and CG) were clinically assessed and laboratory assays were carried out within 1 month after their clinical examination to define their metabolic profile: type 2 diabetes with or without treatment, hypothyroidism with or without treatment, arterial blood pressure, lipid profile (HDL-cholesterol and triglyceridemia), fasting glycaemia and abdominal circumference.

Blood was drawn from participants after an overnight fasting period, and glucose, HDL, LDL, and triglycerides were measured enzymatically by routine techniques in each centre. Waist circumference was measured at the end of a normal expiration, in a horizontal plane around the abdomen at the level of the iliac crest, parallel to the floor.

Patients with SLE were also assessed on demographic, clinical, therapeutic, disease activity and cumulative damage parameters.

Classification of the MS

MS was defined according to the criteria by the AHA/NHLBI Scientific Statement, 2005.[2] Patients were diagnosed with MS when they met at least three of the following criteria: arterial hypertension (≥130 mmHg systolic blood pressure, ≥85 mmHg diastolic blood pressure or drug treatment for hypertension), increased fasting blood glucose (≥100 mg/dl or drug treatment for diabetes), reduced 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 hypertriglyceridemia) and increased waist circumference (≥102 cm in men, ≥88 cm in women).

Variables

Along with the MS components, the following variables were also considered in patients with SLE: age at the moment of enrolment in the study, gender, disease duration (period between SLE diagnosis and enrolment), hypothyroidism, nephrotic syndrome and menopause. Activity of the disease was assessed through the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[28] and cumulative damage through the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI).[29]

Furthermore, the following therapeutic variables were assessed: administration (at any time of the disease and at present), maximum oral dose (mg) excluding methylprednisolone pulses, duration of the treatment (cumulative time in years) and cumulative dosage (g) of prednisone or equivalent medication at enrolment in the study as well as application of methylprednisolone pulse therapy (whether the patient received it or not). Administration (at any time of the disease and at present), duration of the treatment (months) and cumulative dose (g) of hydroxychloroquine (HCQ), and administration and cumulative dosage of other immunosuppressive drugs (methotrexate, azathioprine and cyclophosphamide) were also considered.

Statistical methods

Statistical analyses were carried out in three steps. The first one, descriptive and explanatory, compared the prevalence of the MS among the populations studied, their demographic parameters and the frequency of each of the MS components using descriptive analysis

and one-way ANOVA. A second step compared demographic, clinical and therapeutic characteristics of lupus patients with or without MS using the χ^2 test or Fischer's exact test for categorical variables and non-impaired Student's *t*-test or Mann–Whitney test for continuous variables. Finally, a logistic regression analysis was carried out in a third step. In our case, clinical and therapy variables with assumed clinical relevance or with significance in the univariate analyses were entered into the respective regression analysis.

All analyses used a 5% two-sided significance level and were performed using R Project statistical computing.[30,31]

Results

The demographic characteristics of the 147 patients with SLE and the 119 patients with CG are given in Table 1. Prevalence among females was predominant and similar for both groups (89 vs 86%, respectively). The mean disease duration in the SLE group was 8.8 ± 6.9 years.

Differences between patients with SLE and control patients

The SLE group was significantly younger compared with control patients (37.2 ± 12.3 vs 43.2 ± 13.6 years; $P < 0.0001$). Patients with SLE presented a significantly higher prevalence of the MS (28.6%, CI 95%: 21.4–36.6) compared with control patients (16%, $P = 0.0019$).

When comparing MS components among the groups, patients with SLE showed a significantly higher frequency of arterial hypertension than the CG (43 vs 25%, $P = 0.004$). Surprisingly, control patients demonstrated a higher prevalence of hyperglycaemia (glucose ≥100 mg/dl or treatment) compared with the SLE group (25 vs 10%, $P = 0.003$). However, the frequency of diabetes mellitus was the same in both groups (4%). The remaining MS components did not show any difference (Table 1).

When we analysed the frequency of MS in SLE and control patients younger than 40 years, we observed that the frequency was increased in patients with SLE (40 vs 29%, $P < 0.02$).

Differences between patients with SLE with or without MS

Univariate analysis, comparing characteristics of patients with SLE according to the presence of MS, (Table 2) showed that patients with MS were older (41.7 ± 12.3 vs 35.2 ± 11.8 years old, $P = 0.0036$) and had a higher frequency of diabetes mellitus (15 vs 0%, $P < 0.0001$). No significant differences were observed regarding duration of SLE (9.9 ± 7.04 vs 8.3 ± 6.9 years, P = NS) or SLEDAI score (4 ± 4.7 vs 3.14 ± 4.4, P = NS). However, the cumulative damage score (SDI) was significantly higher in patients with MS (1.52 ± 1.48 vs 0.55 ± 1.01, $P = 0.003$). Regarding therapeutic variables, patients with MS presented higher daily dosage, higher cumulative dosage and higher maximum dose of prednisone or its equivalents as well as a higher prevalence of methylprednisolone pulse therapy, although this was not statistically significant. HCQ administration was significantly higher in patients without MS (87 vs 69%, $P = 0.02$). Logistic regression included age, therapeutic variables and damage indices. This is the model that best explains probability of MS occurrence in this population (Table 3). The variables independently associated with MS with highest significance ($P < 0.05$) were cumulative damage (SDI) with positive relationship (OR 1.98, CI 95% 1.11; 3.55) and the use of HCQ with negative relationship (OR 0.13, CI 95% 0.03; 0.68). Sensibility and specificity were also calculated for this model with a percentage of 70 and 84, respectively.

Table 1 Demographic characteristics of SLE and controls subjects and frequency of metabolic syndrome components

	SLE (n = *147*)	*Control group* (n = *119*)	P *value*
Gender, female (%)	89	86	NS
Age, mean (years)	37.2 ± 12.3	43.2 ± 13.6	<0.0001
Disease duration, mean (years)	8.81 ± 6.9	—	—
Metabolic syndrome (%)	28.6[a]	16	0.0019
High waist circumference (%)	48.5	46	NS
Low HDL or treatment (%)	41	36	NS
TG > 150 mg/dl or treatment (%)	39	27	NS
Glucose ≥ 100 mg/dl or treatment (%)	10	25	0.003
Hypertension or treatment (%)	43	25	0.004

Abbreviations: NS: not significant; HDL: high-density lipoprotein; TG: triglycerides.
[a]SLE: 28.6 (CI 95%: 21.4–36.6).

Table 2 Characteristics of patients with SLE according to the presence or absence of the metabolic syndrome (n = 147)

	Metabolic syndrome		
Features	*Yes* (n = *41*)	*No* (n = *106*)	P *value*
Age, mean (years)	41.7 ± 12.3	35.2 ± 11.8	0.0036
Disease duration, mean (years)	9.93 ± 7.04	8.3 ± 6.93	NS
SLEDAI score, mean	4 ± 4.72	3.14 ± 4.43	NS
SDI score, mean	1.52 ± 1.48	0.55 ± 1.01	0.003
Diabetes mellitus (%)	15	0	<0.0001
Postmenopausal status (%)	33	18	NS
Hypothyroidism (%)	29	13.5	0.03
Prednisone[a], current daily dose, mean (mg/d)	7 ± 8.8	4.6 ± 5.9	NS
Prednisone[a], cumulative dose, mean (g)	23.4 ± 29.9	16.25 ± 18.8	NS
Prednisone[a], maximum oral dose, mean (mg)	44.9 ± 19.5	43.5 ± 21.8	NS
Intravenous methylprednisolone pulses (%)	39	42	NS
Prednisone[a], treatment duration, mean (months)	53.7 ± 62.7	61.25 ± 74.8	NS
Hydroxychloroquine use (%)	69	87	0.02
Hydroxychloroquine, cumulative dose, mean (g)	279.7 ± 336	364.2 ± 425.5	NS
Hydroxychloroquine, treatment duration, mean (months)	33.9 ± 45.6	34.8 ± 34.1	NS
Immunosuppressive agents (%)	75	68.5	NS

Abbreviations: NS: not significant; SLEDAI: systemic lupus erythematosus disease activity index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
[a]Prednisone or equivalent.

Figure 1 shows the probability of MS according to predictor variables. It can be observed that the use of HCQ had a negative effect on the presence of MS while SDI score showed a positive effect.

Discussion

This is the first study in Argentina that assesses the prevalence of MS in patients with SLE, which was higher when compared with control people with non-inflammatory disease. This condition that predisposes to atherosclerotic disease could have an important influence on the morbidity and mortality of our patients and should be routinely examined for early detection. At present, there exists controversy about the usefulness and efficacy of the different MS definitions. However, the latest AHA/NHLBI[2] definition from 2005 is easier to apply, stricter in the definition of parameters such as hyperglycaemia and includes treatment of hypertension, hyperlipidemia and hyperglycaemia in the classification. This could also explain the different findings published on MS in patients with SLE. Chung, *et al.*[20] found an MS prevalence in patients with SLE of 29.4% using the NCEP ATP III definition and a 32.4% prevalence defining MS on the same patients according to WHO standards.[32,33] The latter includes insulin-resistance as a criterion through determination of the HOMA index (homeostasis model assessment). MS prevalence detected by El Magadmi, *et al.*[19] and Bultink, *et al.*[21] was of 18 and 16%, respectively, and in both cases, the authors applied the NCEP ATP III criteria. Zonana-Nacach, *et al.*[26] recently found a similar MS frequency in SLE and RA patients in Mexico (17.7%). The differences may be due to the different ethnic groups, parameter not considered in our study.

To our knowledge, the only publication on MS in patients with SLE that applied the same definition as used in our study was that by Negrón, *et al.*[25] who found a high prevalence of MS in Puerto Rican

Table 3 Logistic regression analysis of factors associated with metabolic syndrome

	Coefficient estimate (βi)	*Standard error* (*SE*)	P *value*	*Odds ratio*	[*CI 95%*]
Intercept	−1.524	1.187	0.199		
Age	0.053	0.029	0.072	1.054	0.99–1.12
HCQ use	−2.007	0.827	0.015	0.13	0.03–0.68
SDI	0.683	0.297	0.021	1.98	1.11–3.55
CphTime	−0.085	0.050	0.090	0.92	0.83–1.01
PDNTime	−0.003	0.005	0.517	0.99	0.98–1.01
HCQTime	0.011	0.010	0.276	1.01	0.99–1.03

Abbreviations: HCQ use: hydroxychloroquine use at any time; SDI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; CphTime: cumulative time of cyclophosphamide; PDNTime: prednisone treatment duration (cumulative time); HCQTime: hydroxychloroquine treatment duration (cumulative time).

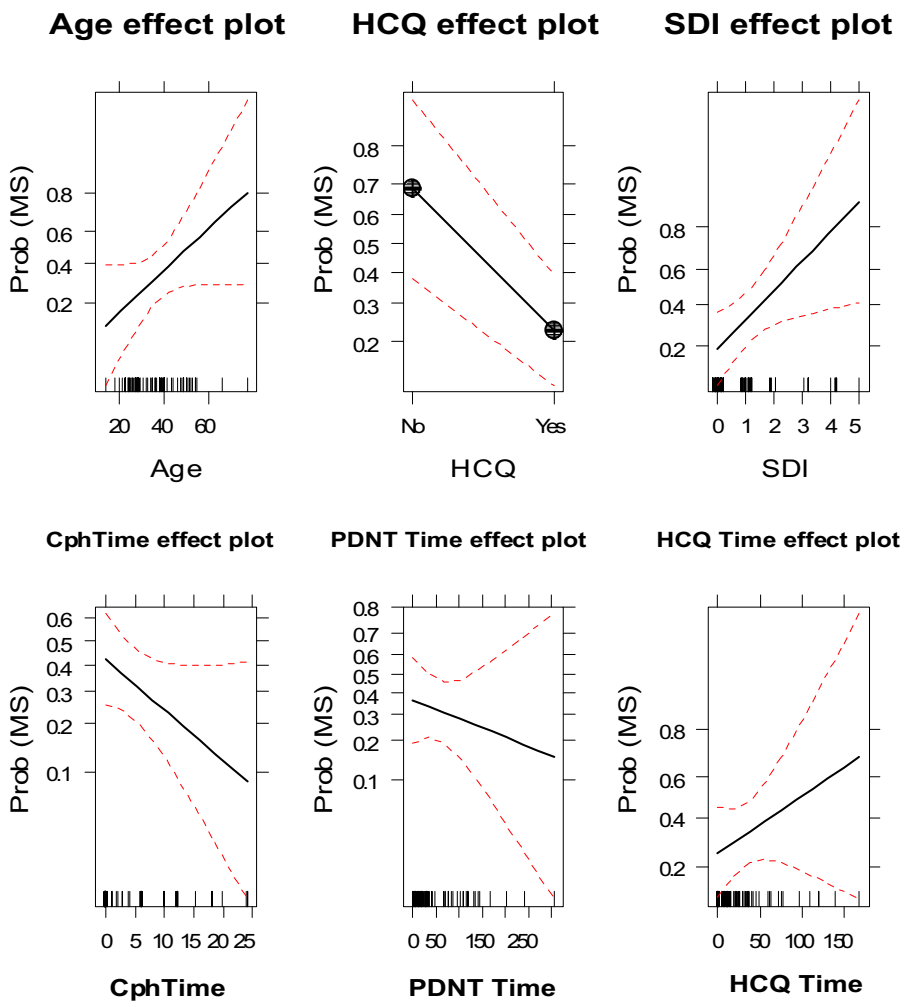

Figure 1 Plot of effects of the factors on the response variable (MS). HCQ use, hydroxychloroquine use at any time; SDI, Systemic Lupus International Collaborating Clinics/ACR Damage Index; CphTime, cumulative time of cyclophosphamide; PDNTime, prednisone treatment duration (cumulative time); HCQTime, hydroxychloroquine treatment duration (cumulative time).

patients with lupus (38.2%), even though a CG was not included in this study.

Our patients with SLE were younger than those in the CG, but patients with MS were older, coinciding with prior publications.[20,25] When comparing MS components, only hypertension was relevant. Chung, *et al.*[20] also found a higher arterial hypertension frequency in patients with SLE compared with controls, although their definition of MS and the hypertension component differed from ours. The frequency of hypertensive patients with lupus in our study (43%) was similar to that previously described by Urowitz, *et al.*[34] (42%) during the period 1996–2001. The study discussed the need to correctly adjust hypertension treatment as a preventive measure against future coronary events in patients with SLE.

Although patients with MS showed a similar SLE follow-up period, they presented a higher cumulative damage index than those without MS, while, contrary to Negrón, *et al.*,[25] the SLEDAI score was similar for both groups. Even though laboratory parameters that express active SLE were associated with MS in previous studies,[20,21,25] we believe that it would be more adequate to carry out prospective monitoring of these parameters and not only a cross-sectional study at a certain moment of the disease. In our opinion, the presence of MS in patients with SLE would reflect the intensity and persistence of the inflammatory response in time. Therefore, the analysis of our results probably manifests a strong and independent association between the presence of MS and the cumulative damage score (SDI), but not with SLEDAI.

Possibly, the most interesting finding of our study is the effect of specific SLE treatment on MS. Although not significant, we found that patients with SLE and MS had received corticosteroid treatment for a shorter

cumulative period of time than those without MS and they had received a similar cumulative dose of prednisone. These findings add more information to the controversial role that steroids play on metabolism and treatment of CVD. Posadas-Romero, *et al.*[35] described that only 15.6% of the variations in insulin levels could be explained by the prednisolone dose administered to their paediatric patients with SLE. Roman, *et al.*[12] found that lupus patients with carotid plaques received lower daily steroid doses. Bruce[36] described a possible dual role of steroids: at a low dose, suppression of the inflammatory response would favour vasculature, but at a high dose, adverse metabolic effects would predominate. None of the recent studies on MS and SLE[19,20,25] found any association with corticosteroid administration, except for Bultink, *et al.*[21] who found an independent association between the number of MS components (MS score) and methylprednisolone pulse therapy antecedents. This differs with our results; our patients with or without MS had received a similar frequency of steroid pulse therapy.

In our patients with SLE, anti-malarial agents appeared as a protective factor against the presence of MS during the logistic regression analysis. These findings differ from previous studies on MS in patients with SLE[19–21,25,26] because none of these authors found a possible association between MS and anti-malarial drugs. However, Sabio, *et al.*[23] found less frequency of HCQ intake among patients with SLE with MS compared with controls from southern Spain. The beneficial effect of HCQ on lipid and glucose metabolism,[37–40] CVD, cumulative damage[41] and mortality[42,43] in patients with SLE has already been studied exhaustively. However, it is not already clear how the HCQ contributes to reduce the risk of vascular events, and in accordance with Sabio, *et al.*, the mechanisms of protection against MS are presumably multifactorial. Our results of the influence of treatment with steroids and anti-malarial drugs in lupus patients with MS help to support the hypothesis already formulated that, since atherosclerosis is an inflammatory disease, specific treatment directed towards the SLE would help to prevent alterations in the metabolism and consequently avoid posterior cardiovascular events.

A limitation to the current study is the fact that presence of associated CVD was not assessed, which would have helped analyse the real importance of detection of MS as promoter of future vascular damage in patients with SLE. However, this first analysis of the MS in Argentinean lupus patients allows us to point out chronic inflammation as one of the contributors to MS, and maybe the immunomodulator or immunosuppressive treatment of SLE as well as the elimination of classical risk factors may reduce CVD morbidity and mortality in the future.

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