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Increased Insulin Resistance and Metabolic Syndrome Frequency in Brazilian Patients with Systemic Lupus Erythematosus: Comparison between Active and Inactive Disease

Aumento da frequência de Resistência à Insulina e Síndrome Metabólica em pacientes brasileiros com Lúpus Eritematoso Sistêmico: comparação entre doença ativa e não ativa

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Abstract

Patients with systemic lupus erythematosus (SLE) have higher insulin resistance (IR) and metabolic syndrome (MetS) prevalence than the general population. However, to date, IR and MetS prevalence in active and inactive disease have not been reported. The objectives of this study were to verify the frequency of IR and MetS in Brazilian patients with SLE and to analyze whether disease activity interferes with the aforementioned conditions. The study included 130 controls and 74 SLE patients. SLE patients were divided in active (36 patients) and inactive (38 patients) disease. IR frequency was verified in 51.35% in patients with SLE and 29.23% in the control group (p=0.0017, OR: 2.556, IC 95%: 1.413-4.621), whereas MetS frequency was 33.78% in patients with SLE and 13.08% in the control group (p<0.0001, OR=4.644, CI 95%: 2.644-9.625). IR was verified in 63.89% patients with active SLE and in 39.47% patients with inactive SLE (OR: 2.781, IC 95%: 1.568-4.932, p=0.0004), whereas 41.67% patients with active SLE met the criteria for MetS compared with 26.32% with inactive SLE (OR: 2.061, IC 95%: 1.133-3.748, p=0.0169). Body mass index and corticosteroids use significantly increased in the active group. This study reinforces the higher risk for developing IR and MetS in patients with SLE, especially in those with active disease, and support the role of IR and corticosteroid use as the main links between disease activity and MetS.

Key Indexing Terms: Lupus Erythematosus. Systemic; insulin. Metabolic Diseases.

Resumo

Pacientes com Lúpus Eritematoso Sistêmico (LES) tem maior prevalência de resistência à insulina (RI) e síndrome metabólica (SM) do que a população em geral. No entanto, atualmente, a frequência de RI e SM em pacientes com doença inativa ou em atividade não tem sido reportada. Os objetivos deste estudo foram verificar a freqüência de RI e SM em pacientes brasileiros com LES e avaliar se a atividade da doença interfere com essas duas condições. O estudo incluiu 130 indivíduos controles e 74 pacientes com LES. Pacientes com

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LES foram divididos em doença ativa (36 pacientes) e não ativa (38 pacientes). A RI foi verificada em 51,35% de pacientes com LES e apenas em 29,23% do grupo controle (p=0.0017, OR: 2.556, IC 95%: 1.413-4.621), enquanto a SM foi verificada em 33,78% de pacientes e 13,08% do grupo controle (p<0.0001, OR=4.644, CI 95%: 2.644-9.625). RI foi verificada em 63,89% dos pacientes com LES ativo e em 39,47% de pacientes com doença não ativa (OR: 2.781, IC 95%: 1.568-4.932, p=0.0004), enquanto 41,67% pacientes com LES ativo apresentaram critérios para SM comparado a apenas 26,32% com LES não ativo (OR: 2.061, IC 95%: 1.133-3.748, p=0.0169). O índice de massa corporal e o uso de corticosteroides foi significativamente maior no grupo com doença ativa. Este estudo reforça o risco aumentado de desenvolvimento de RI e SM em pacientes com LES, especialmente naqueles com doença ativa e corrobora com o papel da RI e da corticoterapia como principais mediadores entre a atividade da doença e a SM.
Palavras-Chave: Lúpus Eritematoso Sistêmico. Insulina. Doença metabólica.

Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterized by multisystem organ involvement and by high titers of autoantibodies against several nuclear and cytoplasmatic antigens (OATES, 2010).

Whereas the impact of infections and active disease on mortality has diminished dramatically over the years, due to intensive treatment, cardiovascular disease (CV) has emerged as the leading cause of death in these patients (BERNATSKY et al. 2006). Increased risk of coronary heart disease (CHD) in SLE is not explained by the classic CHD risk factors (ASANUMA et al. 2003; ROMAN et al. 2003; EL-MAGADMI et al. 2006).

Reaven (1988) have proposed the concept of metabolic syndrome (MetS) in 1988. Since then many researchers believe that insulin resistance (IR) is the pathophysiological process underlying the clustering of CV risk factors in MetS and that IR increases the values of clinical diagnosis of MetS (HANLEY et al. 2002; REILLY et al. 2004). Therefore, IR and MetS are clearly strong candidates to justify the increase in CHD in patients with SLE.

Several studies have demonstrated that SLE patients have more severe IR compared with the general population (EL-MAGADMI et al. 2006; SADA et al. 2006; CHUNG et al. 2007; CHUNG et al. 2009). IR may contribute to the pathogenesis of MetS through hyperglycemia, compensatory hyperinsulinemia, and imbalanced insulin action. Among them, hyperinsulinemia seems to be the most important factor (SIDIROPOULOS; KARVOUNARIS; BOUMPAS 2008). Chung et al. (2007) found a prevalence of 44.1% of insulin resistance in patients with SLE. Several studies have also shown high MetS prevalence in patients with SLE in developed countries. MetS classification according to National Cholesterol Educational Program (NCEP ATP-III) showed a prevalence of 16% in Netherlands (BULTINK et al. 2008), from 17% to 20% in Spain ZONANA-NACACH et al. 2008; SABIO et al. 2008), 18% in the United Kingdom (EL-MAGADMI et al. 2006), and 29.4% and 32.4% in the United States (CHUNG et al. 2007), when the authors used NCEP ATP-III or World Health Organization (WHO) classification, respectively. The later classification requires direct determination of insulin resistance (PARKER; BRUCE 2010). In Italy (VADACCA et al. 2009), also using World Health Organization (WHO) classification, it was found a prevalence of 28%. In Latin American countries, this scenario is not very different, and MetS classification according to American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) showed a prevalence which ranged from 28.6% in Argentina (BELLOMIO et al. 2009) to 38.2% in Puerto Rico (NEGRÓN et al. 2008). In Brazil, a South American emerging country with a continental dimension, classification according to NCEP ATP-III reports have found a prevalence of 20% in Northeast (AZEVEDO; GADELHA; VILAR 2007), and 32.1% in Southeast (TELLES et al.2010).

There are several mechanisms by which higher severity and frequency of IR in SLE patients could be explained, such as obesity, inflammatory markers,

and the medication to treat SLE patients, especially glucocorticoids. However, studies which have focused on lupus disease activity, another mechanism that could contribute to insulin resistance and MetS, has been scarce and controversial. We are aware of only one study with SLE pediatric patients in which they were classified in active and inactive disease (POSADAS-ROMERO et al. 2004). Studies have been found contradictory results in the association between MetS and active SLE. Association between MetS and disease activity has been reported in some reports (BULTINK et al. 2008; SABIO et al. 2008; TELLES et al.2010), but not in others (EL-MAGADMI et al. 2006; CHUNG et al. 2007).

Although some studies have verified a correlation between IR and MetS with disease activity, little is known about disease activity participation in those two conditions. Therefore, the objectives of the present study were to verify the frequency of IR and MetS in patients with SLE and to analyze whether disease activity interferes with the aforementioned conditions.

Subjects and Methods

Subjects

The study included 204 subjects. One hundred and thirty healthy individuals were selected from among blood donors of the University Hospital and 74 patients with SLE were selected from among the ambulatory of Rheumatology of the University Hospital of Londrina, Paraná, Brazil, to participate in the study. They were paired by sex, age, ethnicity, and body mass index (BMI). Systemic Lupus Erythematosus was diagnosed using the American College of Rheumatology (ACR) 1997 revised criteria (HOCHBERG 1997). Patients with SLE were also divided in two groups: with active disease (n=36) or inactive disease (n=38). The following parameters were used to classify SLE as active: SLE Disease Activity Index (SLEDAI) score ≥ 6 (BOMBARDIER et al. 1992), and/or decreased C3 (<90mg/dL) and/or decreased C4 complement (< 10 mg/dL), and/or positive anti-dsDNA (titre ≥ 1/10) (NUTTALL et al. 2003). MetS was defined following the Adult Treatment Panel III criteria (JACOBS 2001), when three of the following five characteristics were confirmed: 1) Abdominal obesity: waist circumference ≥ 102 cm in men and ≥ 88 cm in women; 2) Hypertriglyceridemia ≥ 150 mg/mL; 3) Low levels of HDL cholesterol: ≤ 40 in men and ≤ 50 mg/dL in women; 4) High blood pressure: ≥ 130/85 mmHg; and 5) High fasting glucose: ≥ 110mg/dL.

Information on lifestyle factors and medical history were obtained at clinical evaluation. Disease duration, organ involvement, values of C3 and C4 complement, anti-double-stranded DNA (anti-dsDNA), and non-steroid anti-inflammatory drugs, corticosteroids, antimalarials, oral contraceptives, and antihypertensive medications were recorded for each patient. All patients were receiving prednisone at the time of inclusion, thus predinisone-equivalent calculation was not required. They had been taking the same prednisone dose at least for the past 4 months. No patient with SLE presented proteinuria. Nutritional status of patients was similar to that of the control group. None of the subjects were receiving a specific diet. The individuals of both groups did not drink alcohol regularly. None of the participants in the study presented heart, thyroid, renal, hepatic, gastrointestinal or oncological diseases, and none were receiving estrogen replacement therapy, drugs for hyperlipidemia, hyperglycemia or antioxidant supplements. All patients gave written informed consent, and the study protocol was fully approved by the Ethical Committee of the University of Londrina, Paraná, Brazil.

Anthropometric and Blood Pressure Measurements

Body weight was measured to the nearest 0,1 kg by using an electronic scale, with individuals

wearing light clothing, but no shoes, in the morning.; height was measured to the nearest 0,1 cm by using a stadiometer. Body mass index was calculated as weight (kg) divided by height (m) squared. Three blood pressure measurements taken with a minute interval between them after the subject had been seated were recorded. The mean of these measurements was used in the analysis. We considered the current use of antihypertensive medication as an indication of high blood pressure.

Biochemical and Immunological Biomarkers

After fasting for 12 hours, the patients underwent the following laboratory blood analysis: glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triacylglycerol, uric acid, evaluated by a biochemical auto-analyzer (Dimension Dade AR Dade Behring, Deerfield, IL, USA), using Dade Behring® kits; Plasma insulin levels were determined by plasma insulin levels were determined by chemiluminescence microparticule immunoassay (Architect, Abbott Laboratory, Abbott Park, IL, USA). The homeostasis model assessment insulin resistance (HOMA-IR) was used as a surrogate measurement of insulin sensitivity (HAFFNER; MIETTINEN; STERN 1997). HOMA-IR = insulin fasting (μU/ml) X glucose fasting (nmol/L) / 22.5. Insulin resistance was considered when HOMA-IR ≥ 2.114 (CHUNG et al. 2008).

Serum complement factors C3 and C4 levels and hsCRP (highly sensitive CRP) were measured using a nephelometric assay (Behring Nephelometer II, Dade Behring, Marburg, Germany). Anti-double-stranded DNA (anti-dsDNA) antibodies were determined by immunoflurescence using Crithidia lucilliae kinetoplast assay.

Statistical analysis

Distribution of sex, race, and smoking was analyzed with Fisher's exact test or chi-square test. Comparisons between patients with active or inactive SLE were done using the Mann-Whitney test and data were expressed as the median (25-75 percentiles). Correlations were evaluated by Spearman's rank correlation. It was performed a multivariate regression analysis with a view to determining which variables showed the strongest relationship with activity disease. The results were considered significant when $p<0.05$. A statistical analysis program (Graph Pad Prism version 4.0) was used for evaluations.

Results

Clinical characteristics of the patients with SLE are shown in table 1. The majority of patients did not present clinical signs and symptoms of disease. In relation to the control group, patients with SLE presented significantly higher systolic ($p=0.006$) and diastolic ($p=0.0007$) blood pressure, triacylglycerol ($p=0.039$) levels, insulin ($p<0.0001$) levels, and HOMA-IR ($p=0.0006$), and significantly lower blood glucose levels ($p=0.017$) (Table 2). Patients with SLE and the control group had no differences in WC, and serum total cholesterol, HDL cholesterol, LDL cholesterol, CRP, and adiponectin concentrations (Table 2).

Table 1 - Clinical and laboratory profile of patients with Systemic Lupus Erythematosus (SLE)

	SLE Patients (n=74)	Frequency (%)
Disease Duration (years/SD)*	8.5 (4.0-12.3)	---
SLEDAI Score*	2 (0-4)	---
SLEDAI Score > 6	14	10.4
Anti-dsDNA Positive	15	11.1
C3 (<90mg/dL)	13	9.6
C4 (<10 mg/dL)	5	3.7
	Therapy	
Prednisone	71	95.9
Antimalarials	44	54.5
Current Immunosuppressive	22	29.7
ACE inhibitors	9	12.2

* Data are expressed median (minimum – maximum). SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme

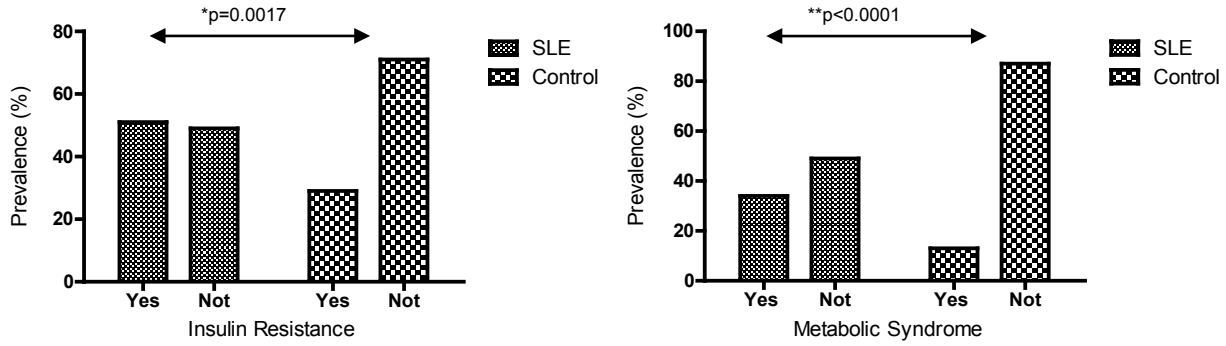
Table 2 - Clinical and laboratory characteristics of patients with systemic lupus erythematosus (SLE) and controls.

	Control (n=130)	SLE (n=74)	P value
Gender (male/female)	9/121	7/67	0.457
Caucasian/not Caucasian	106/24	59/15	0.752
Age (years)	39.0 (31.0-46.0)	42.0 (29.0-51.0)	0.415
BMI (kg/m^2)	25.00 (22.91-28.16)	26.84 (22.86-30.86)	0.101
WC (cm)	90.0 (84.5-100.0)	93.0 (84.0-104.5)	0.423
Systolic Blood Pressure (mmHg)	110.0 (101.0-125.0)	119.5 (109.5-130.0)	0.006
Diastolic Blood Pressure (mmHg)	71.0 (65.5-80.0)	78.0 (70.5-85.5)	0.0007
Triacylglicerol (mg/dL)	93.0 (68.0-125.0)	106.0 (78.0-152.0)	0.039
Cholesterol (mg/dL)	196.0 (173.0-218.0)	188.0 (162.0-210.0)	0.127
HDL cholesterol (mg/dL)	55.0 (48.0-66.0)	53.0 (45.0-60.0)	0.197
LDL cholesterol (mg/dL)	116.0 (94.5-137.0)	107.0 (88.5-127.5)	0.094
Glucose (mg/dL)	88.0 (83.0-95.0)	84.0 (80.0-92.5)	0.017
Insulin (µU/mL)	7.20 (5.15-10.40)	9.90 (7.30-13.10)	<0.0001
HOMA-IR	1.60 (1.13-2.32)	2.20 (1.55-2.96)	0.0006

Mann-Whitney test. Data are expressed median (minimum-maximum). BMI, body mass index; WC, waist circunference; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance.

IR frequency was verified in 51.35% in patients with SLE and 29.23% in the control group (p=0.0017, OR: 2.556, IC 95%: 1.413-4.621), whereas MetS prevalence was 33.78% in patients with SLE and 13.08% in the control group (p<0.0001, OR=4.644, CI 95%: 2.644-9.625) (Figure ¬¬1).

Figure 1 - Insulin Resistance and Metabolic Syndrome in southern Brazilian patients with systemic lupus erythematosus and control subjects.



Chi-square test. *OR=2.556 (CI 95%: 1.413-4.621, p=0.0017). **OR=4.644 (CI 95%: 2.240-9.625, p<0.0001). OR (Odds Ratio).

Patients with active or inactive disease were paired by gender, age, and ethnicity. Patients with active disease had higher BMI (p=0.003) and WC (p=0.035) when compared to control subjects. Multivariate analysis showed association between BMI and disease activity (p=0.0184), but not with WC. As expected, patients with active SLE were taking higher prednisone doses (p=0.041), had higher SLEDAI score (p<0.0001), and presented serum C3 (p<0.0001) and C4 (p=0.0002) lower concentrations (Table 3). Patients with active SLE presented significantly higher serum insulin concentration (p=0.048) and HOMA-IR (p=0.030) and a trend to lower blood glucose levels (0.058) with respect to patients with inactive SLE. There were no differences between the groups with regard to systolic and diastolic blood pressure, triacylglycerol, total cholesterol, HDL cholesterol, and LDL cholesterol concentrations (Table 3).

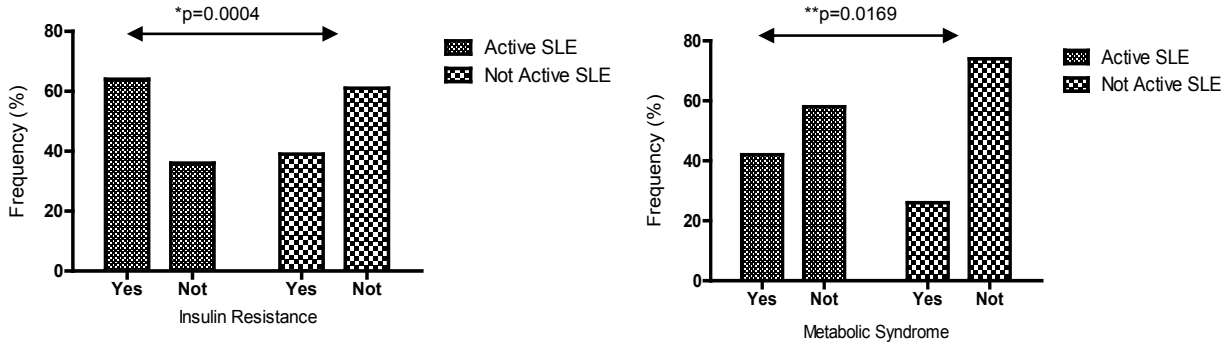
Table 3 - Disease activity parameters, anthropometric measurements, and metabolic biomarkers, and insulin resistance and metabolic syndrome prevalence in active and inactive SLE patients

Parameters	Inactive SLE (n = 38)	Active SLE (n = 36)	P value
Gender (male/female)	4/34	3/33	1.000
Caucasian/not Caucasian	31/7	28/8	0.684
Disease Duration (years)	7.0 (4.0-10.0)	10.0 (4.75-15.5)	0.201
Age (years)	37.0 (28.5-52.0)	43.0 (29.5-50.5)	0.6188
BMI	24.5 (21.8-27.8)	28.8 (26.1-32.9)	0.003
WC (cm)	90.0 (83.0-94.0)	101.5 (84.0-107.0)	0.035
Antimalarials (Yes/Not)	20/18	21/15	0.619
Prednisone (mg/day)	5.50 (5.00-15.00)	12.5 (7.50-20.0)	0.041
SLEDAI	0 (0-0)	4 (2-6)	<0.0001
C3 (mg/dL)	121.0 (113.5-140.5)	99.2 (87.7-118.0)	<0.0001
C4 (mg/dl)	24.1 (18.7-28.7)	15.9 (13.4-21.3)	0.0002
BMI (kg/m^2)	25.74 (22.66-29.27)	28.69 (22.60-32.87)	0.068
Systolic Blood Pressure (mmHg)	120.0 (108.5-129.0)	119.0 (109.5-132.0)	0.741
Diastolic Blood Pressure (mmHg)	78.0 (70.0-85.0)	78.5 (73.0-88.5)	0.305
Triacylglicerol (mg/dL)	102.0 (71.5-144.0)	123.0 (85.5-160.0)	0.114
Cholesterol (mg/dL)	193.5 (168.0-204.5)	182.0 (161.0-216.5)	0.986
HDL cholesterol (mg/dL)	52.5 (45.7-68,8)	52.5 (43.0-59.0)	0.593
LDL cholesterol (mg/dL)	107.0 (91.5-127.5)	110.0 (85.0-133.0)	0.880
Glucose (mg/dL)	86.5 (81.5-94.5)	83.0 (80.0-89.0)	0.058
Insulin (µU/mL)	8.90 (7.30-11.20)	11.50 (7.25-16.45)	0.048
HOMA-IR	1.97 (1.52-2.31)	2.43 (1.59-3.53)	0.030

Mann-Whitney test. Data are expressed median (minimum-maximum). BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance;

IR was verified in 63.89% patients with active SLE and in 39.47% patients with inactive SLE (OR: 2.781, IC 95%: 1.568-4.932, p=0.0004) (Figure 2), whereas 41.67% patients with active SLE met the criteria for metabolic syndrome compared with 26.32% with inactive SLE (OR: 2.061, IC 95%: 1.133-3.748, p=0.0169) (Figure 2).

Figure 2 - Insulin resistance and Metabolic Syndrome in southern Brazilian with systemic lupus erythemathosus (SLE) active or inactive.



*OR: 2.781 (IC 95%: 1.568-4.932, p=0.0004); **OR: 2.061 (IC 95%: 1.133-3.748, p=0.0169). OR (Odds Ratio).

Discussion

The major findings of the current study are that patients with SLE have an increased risk for developing IR (2.5 times) and MetS (4.6 times) than a control group. In addition, even a mild to moderate activity in patients with SLE is associated with an increased risk for developing IR (2.8 times) and MetS (2.1 times) compared with inactive SLE patients. The data from the present study permit to suggest that disease activity shown by increased SLEDAI score and decreased serum C3 and C4 levels has also an important role in the development of IR in SLE patients.

Although previous studies that have also demonstrated enhanced levels of fasting insulin (EL-MAGADMI et al. 2006; SADA et al. 2006; CHUNG et al. 2007; CHUNG et al. 2009), enhanced prevalence of IR (CHUNG et al. 2007), and MetS (PARKER; BRUCE 2010) in SLE patients, to our knowledge the present study showed the highest frequency of MetS in patients with SLE compared with these studies. The higher IR and MetS frequency which were found in the present study may be explained by the following reasons: firstly, many studies (ZONANA-NACACH et al. 2008; TELLES et al.2010; NEGRÓN et al. 2008) have verified that lupus patients was associated with lower income, a finding which was also verified in most of our patients. Secondly, as MetS prevalence is increasing over time in the general population (GRUNDY 2008), it is likely that it is also increasing in SLE patients.

Of note, SLE patients presented lower blood glucose levels, but higher insulin and HOMA-IR levels in relation to control subjects. The same trend was observed when active SLE patients were compared to inactive SLE patients. It can be assumed that metabolic derangement in these patients with inactive or lupus with mild activity are in an initial phase, as increased insulin production is still sufficient to maintain blood glucose levels within normal range, although insulin resistance shown by HOMA-IR seems to be established. Noteworthy, differently from IR results which showed higher levels in active disease, all components of NCEP ATP-III classification used

in the present study were not different in active or inactive disease despite a higher MetS prevalence, showing the importance of insulin resistance in the development of these components. Our data are in accordance with Reilly et al. (2004) who suggested the use of biomarkers of IR in addition to ATP-III criteria in assessing CV risk.

The present study is in accordance with previous studies, which also have found an association between lupus disease activity and MetS. This association has been shown with SLEDAI score (NEGRÓN et al. 2008; TELLES et al. 2010; KARP et al. 2008), whereas with serum C3 levels, it has been demonstrated inverse (SABIO et al. 2008) and direct association (BULTINK et al. 2008) with MetS. This apparent paradox can be explained because serum C3 and C4 levels may, in some circumstances, act as an acute-phase reactant protein (LOZOVOY et al. 2011). On the other hand, no association between SLE activity and MetS was found by others authors (EL-MAGADMI et al. 2006; CHUNG et al. 2007).

It has been proposed that obesity (CHUNG et al. 2008), corticosteroid therapy (VEGIOPOULOS; HERZIG 2007), and chronic inflammatory process (HOTAMISLIGIL 2000; CAPPER et al. 2004) are involved in metabolic syndrome found in SLE patients. BMI and WC were higher in active disease when compared with inactive disease and multivariate analysis confirmed the association between BMI and disease activity. These data suggest that increased body mass probably due to glicocorticoids use also contributes to increased risk of developing metabolic syndrome in active disease.

The association between glucocorticoids and MetS is controversial. Several reports have shown association between prednisone use above 10 mg/d and MetS (NEGRÓN et al. 2008; GRUNDY 2008; ZONANA-NACACH et al. 2000) or with intravenous prednisolone (BULTINK et al. 2008). However, other reports have not found any association (EL-MAGADMI et al. 2006; CHUNG et al. 2007; TELLES et al. 2010). For example, Posadas-Romero et al. (2004) found that prednisone explained 15.6% in the variance of insulin levels.

An important limitation in this study is our population included patients with SLE with relatively low disease activity, and therefore, our findings may not be applicable to patients with severe active disease. Nevertheless, the main strength of the present study is its original design, which allowed investigating for the first time, to our knowledge, the increased risk of moderately active SLE patients in developing IR and MetS when compared with inactive disease patients.

In conclusion, this study reinforces the higher risk for developing IR and MetS in patients with SLE, especially in those with active disease, and support the role of IR and corticosteroid use as the main links between disease activity and MetS. Routine inclusion of simple indices of IR in SLE patients is strongly suggested as well as non pharmacological and pharmacological measures when necessary to improve insulin sensitivity. The development of selective anti-inflammatory steroids, less susceptible to undesirable metabolic effects, is still awaited.

Acknowledgments

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References

ASANUMA, Y.; OESER, A.; SHINTANI, A. K.; TURNER, E.; OLSEN, N.; FAZIO, S.; LINTON, M. F.; RAGGI, P.; STEIN, C. M. *Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Eng J Med*, Boston, v. 349, p. 2407-2415, 2003.

AZEVEDO, G. D.; GADELHA, R. G.; VILAR. M. J. Metabolic syndrome in systemic lupus erythematosus: lower prevalence in Brazil than in the USA. *Annals of the Rheumatic Diseases*, London, v. 66, n.11, p. 1542, 2007.

BELLOMIO, V.; SPINDLER, A.; LUCERO, E.; BERMAN, A.; SUELDO. R.; BERMAN, H.; SANTANA, M.; MOLINA, M. J.; GÓNGORA, V.; CASSANO, G.; PAIRA, S.; SAURIT, V.; RETAMOZO, G.; ALVARELLOS, A.; CAERIO, F.; ALBA, P.; GOTERO, M.; VELOZO, E. J.; CEBALLOS, F.; SORIANO, E.; CATOGGIO, L.; GARCÍA, M. A.; EIMON, A.; AGÜERO, S. Metabolic syndrome in Argentinean patients with systemic lupus erythematosus. *Lupus*, Houndmills, v. 18, p. 1019-1025, 2009.

BERNATSKY, S.; BOIVIN, J. F.; JOSEPH. J. E.; MANZI, S.; GINZLER, E.; GLADMAN, D. D.; UROWITZ, M.; FORTIN, P. R.;, PETRI, M.; BARR, S.; GORDON, C.; BAE, S. C.; ISENBERG, D.; ZOMA, A.; ARANOW, C.; DOOLEY, M. A.; NIVED, O.; STURFELT, G.; STEINSSON, K.; ALARCÓN, G.; SENÉCAL, J. L.; ZUMMER, M.; HANLY, J.; ENSWORTH, S.; POPE, J.; EDWORTHY, S.; RAHMAN, A.; SIBLEY, J.; EL-GABALAWY, H.; MCCARTHY, T.; ST PIERRE, Y.; CLARKE, A.; RAMSEY-GOLDMAN, R. Mortality in systemic lupus erythematosus. *Arthritis Rheumatology*, Atlanta, v. 54, p. 2550-2557, 2006.

BOMBARDIER, C.; GLADMAN, D. D.; UROWITZ, M. B.; CARON, D.; CHANG, C. H. Derivation of the SLEDAI: a disease activity index for lupus patients. The Committee on prognosis Studies in SLE. *Arthritis Rheumatology*, Atlanta, v. 35, p. 630-640, 1992.

BULTINK, I. E. M.; TURKSTRA, F.; DIAMANT, M.; DIJKMANS, B. A. C.; VOSKUYL, A. E. Prevalence of and risk factors for the metabolic syndrome in women with systemic lupus erythematosus. *Clinical & Experience Immunology,* Pisa, v. 26, p. 32-38, 2008.

CAPPER, E. R.; MASKILL, J. K.; GORDON, C.; BLAKEMORE, A. I. F. Interleukin (IL)-10, IL-1ra and IL-12 profiles in active and quiescent systemic lupus erythematosus: could longitudinal studies reveal patients subgroups of differing pathology? *Clinical & Experience Immunology*, Oxford, v. 138, p. 348-356, 2004.

CHUNG, C. P.; AVALOS, I.; OESER, A.; GEBRETSADIK, T.; SHINTANI, A.; RAGGI, P.; STEIN, C. M. High frequency of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristic and cardiovascular risk factors. *Annals of the Rheumatic Diseases*, London, v. 66, p. 208-214, 2007.

CHUNG, C. P.; OESER, A.; SOLUS, J. F.; GEBRETSADIK, T.; SHINTANI, A.; AVALOS, I.; SOKKA, T. ; RAGGI, P.; PINCUS, T.; STEIN, C. M. Inflammation-associated insulin resistance. *Arthritis Rheumatology*, Atlanta, v. 58, p. 2105-2112, 2008.

CHUNG, C. P. ; LONG, A. G. ; SOLUS, J. F. ; RHO, Y. H.; OESER, A.; RAGGI, P.; STEIN, C. M. Adipocytokines in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. *Lupus*, Houndmills, v. 18, p. 799-806, 2009.

EL-MAGADMI, M.; AHMAD, Y.; TURKIE, W.; YATES, A. P.; SHEIKH, N.; BERNSTEIN, R. M.; DURRINGTON, P. N.; LAING, I.; BRUCE, I. N. Hyperinsulinemia, insulin resistance, and circulating oxidized low density lipoprotein in women with systemic lupus erythematosus. *The Journal of Rheumatology*, Toronto, v. 33, p. 50-56, 2006.

GRUNDY, S. M. Metabolic syndrome pandemic. *Arteriosclerosis Thrombosis and Vascular Biology,* Dallas, v. 28, p. 629-636, 2008.

HAFFNER, S. M.; MIETTINEN, H.; STERN, M. P. The homeostasis model in the San Antonio Heart Study. *Diabetes Care,* New York, v. 20, p. 1087-1092, 1997.

HANLEY, H.; KARTER, A.; FESTA, A.; D'AGOSTINO, R. JR.; WAGENKNECHT, L. E.; SAVAGE, P.; TRACY, R. P.; SAAD, M. F.; HAFFNER, S. Factor analysis of metabolic syndrome using directly measured insulina sensitivity: The Insulin Resistance Atherosclerosis Study. *Diabetes*, New York, v. 51, p. 2642-2647, 2002.

HOCHBERG, M. C. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheumatology*, Atlanta, v. 40, p. 1725, 1997.

HOTAMISLIGIL, G. S. Molecular mechanisms of insulin resistance and the role of the adipocyte. *Internacional Journal of Obesity and Related Metabolic Disorders*, Hampshire, v. 24, p. 23-27, 2000.

JACOBS, D. R. JR. *E*xecutive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and high blood cholesterol in adults (Adults Treatment Panel III). *JAMA*, Chicago, v. 285, p. 2486-2497, 2001.

KARP, I.; ABRAHAMOWICZ, M.; FORTIN, P. R.; PILOTE, L.; NEVILLE, C., PINEAU, C. A.; ESDAILE, J. M. Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? *Arthritis Rheumatology,* Atlanta, v. 59, p.169-175, 2008.

LOZOVOY, M. A. B.; SIMÃO, A. C.; PANIS, C.; ROTTER, M. A.; REICHE, E. M.; MORIMOTO, H. K.; LAVADO, E.; CECCHINI, R.; DICHI, I. Oxidative stress is associated with liver damage, inflammatory status, and corticosteroid therapy in patients with systemic lupus erythematosus. *Lupus,* Houndmills, v. 20, p. 1250-1259, 2011.

NEGRÓN, A. M.; MOLINA, M. J.; MAYOR, A. M.; RODRÍGUEZ, V. E.; VILÁ, L. M. Factors associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico. *Lupus*, Houndmills, v. 17, p. 348-354, 2008.

NUTTALL, S. L.; HEATON, S.; PIPER, M. K.; MARTIN, U.; GORDON, C. Cardiovascular risk in systemic lupus erythematosus-evidence of increased oxidative stress and dyslipidemia. *Rheumatology*, Philadelphia, v. 42, p. 758-762, 2003.

OATES, J. C. The biology of reactive intermediates in systemic lupus erythematosus. *Autoimmunity*, London, v. 43, p. 56-63, 2010.

PARKER, B.; BRUCE, I. N. The metabolic syndrome in systemic lupus erythematosus. *Rheum Dis Clin N Am*, Philadelphia, v. 36, p. 81-97, 2010.

POSADAS-ROMERO, C.; TORRES-TAMAYO, M.; ZAMORA-GONZÁLEZ, J.; AGUILAR-HERRERA, B. E.; POSADAS-SÁNCHEZ, R.; CARDOSO-SALDAÑA, G.; LADRÓN DE GUEVARA, G.; SOLIS-VALLEJO, E.; EL HAFIDI, M. High insulin levels and increased low-density lipoprotein oxidizability in pediatric patients with systemic lupus erythematosus. *Arthritis Rheumatology*, Atlanta, v. 50, p. 160-165, 2004.

REAVEN, G. M. Banting Lecture 1988: *R*ole of insulin resistance in human disease. *Diabetes,* New York, v. 37, p. 1595-1607, 1988.

REILLY, M. P.; WOLFE, M.; RHODES, T.; GIRMAN, C.; MEHTA, N.; RADER, D. J. Measures of insulin resistance add incremental value to the clinical diagnosis of metabolic syndrome in association with coronary atherosclerosis. *Circulation*, Dallas, v. 110, p. 803-809, 2004.

ROMAN, M. J.; SHANKER, B. A.; DAVIS, A.; LOCKSHIN, M. D.; SAMMARITANO, L.; SIMANTOV, R.; CROW, M. K.; SCHWARTZ, J. E.; PAGET, S. A.; DEVEREUX, R. B.; SALMON, J. E. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *The New England Journal of Medicine*, Boston, v. 349, p. 2399-2406, 2003.

SABIO, J. M.; ZAMORA-PASADAS, M.; JIMÉNEZ-JÁIMEZ, J.; ALVADALEJO, F.; VARGAS-HITOS, J.; RODRÍGUEZ DEL AGUILA, M. D.; HIDALGO-TENORIO, C.; GONZALEZ-GAY, M. A.; JIMENEZ-ALONSO, J. Metabolic syndrome in patients with systemic lupus erythematosus from Southern Spain. *Lupus,* Houndmills, v.17, p. 849-859, 2008.

SADA, K. E.; YAMASAKI, Y.; MARUYAMA, M.; SUGIYAMA, H.; YAMAMURA, M.; MAESHIMA, Y.; MAKINO, H.; Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. *The Jornal of Rheumatology,* Toronto, v. 33, p. 1545-1552, 2006.

SIDIROPOULOS, P. I.; KARVOUNARIS, S. A.; BOUMPAS, D. T. Metabolic syndrome in rheumatic diseases: epidemiology, pathophysiology, and clinical implications. *Arthritis Research Therapy,* London, v. 10, p. 207-215, 2008.

TELLES, R. W.; LANNA, C. C. D.; FERREIRA, G. A.; RIBEIRO. A. L. Metabolic syndrome in patients with systemic lupus erythematosus: association with traditional risk factors for coronary heart disease and lupus characteristics. *Lupus*, Houndmills, v. 19, p. 803–809, 2010.

VADACCA, M.; MARGIOTTA, D.; RIGON, A.; CACCIAPAGLIA, F.; COPPOLINO, G.; AMOROSO, A.; AFELTRA, A. Adipokines and systemic lupus erythematosus: relationship with metabolic syndrome and cardiovascular disease risk factors. *Journal of Rheumatology*, Toronto, v. 36, p. 295-297, 2009.

VEGIOPOULOS, A.; HERZIG, S. Glucocorticoids, metabolism and metabolic disease. *Mollecular and Cellular Endocrinology*, Amsterdam, v. 275, p. 43-61, 2007.

ZONANA-NACACH, A.; BARR, S. G.; MADGER, L. S.; PETRI, M. *D*amage in systemic lúpus erythematosus and its association with corticosteroids. *Arthritis Rheumatology*, Atlanta, v. 43, p. 1801-1808, 2000.

ZONANA-NACACH, A.; SANTANA-SAHAGÚN, E.; JIMÉNEZ-BALDERAS, F. J.; CAMARGO-CORONEL, A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. *J Clin Rheumatol,* Baltimore, v. 14, p. 74-77, 2008.

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