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PAPER

Metabolic syndrome in patients with systemic lupus erythematosus: association with traditional risk factors for coronary heart disease and lupus characteristics

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The objective of this study was to determine the frequency of Metabolic Syndrome (MetS) in patients with SLE and to analyze the association of MetS with traditional risk factors for CHD and lupus characteristics. In this cross-sectional study the frequency of MetS was determined according to the National Cholesterol Education Program Adult Treatment Panel III in patients with SLE. The association of MetS with the traditional risk factors for CHD not included in the syndrome definition, and with lupus characteristics was examined. The mean age (sd) of the 162 females patients was 38.8(11.2) years. The frequency of MetS was 32.1%. Abdominal obesity and hypertension were the two most common components of the syndrome (86.5% each) followed by low levels of HDL-cholesterol (84.6%), hypertriglyceridemia (69.2%) and hyperglycemia (15.4%). MetS was significantly associated with older age, family history of CHD, obesity, postmenopausal status, LDL-c $\geq$100mg/dl, and higher Framingham risk score. Lupus characteristics associated with MetS were history of nephrotic proteinuria during follow-up and current cyclophosphamide use, higher modified SLEDAI-2k, higher damage index score (SLICC/ACR), and older age at lupus diagnosis. In the logistic regression analysis, obesity, LDL-c $\geq$100mg/dl, older age at lupus diagnosis, higher damage index and nephrotic proteinuria were independently associated with MetS. We conclude that MetS diagnosis was frequent in patients with lupus. The syndrome was associated not only with traditional risk factors for CHD, confirming the clustering of those risk factors, but also with lupus characteristics. Some of those factors, especially LDL-c $\geq$100mg/dl and age at lupus diagnosis, have been associated with atherosclerosis in lupus patients. *Lupus* (2010) **19,** 803–809.

Key words: cardiovascular disease; cardiovascular risk factors; lupus damage; metabolic syndrome; nephrotic proteinuria; systemic lupus erythematosus

Introduction

Metabolic syndrome (MetS) is a condition characterized by insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia (hypertriglyceridemia and/or hypo-high-density-lipoprotein (HDL)-cholesterolemia), high arterial blood pressure and central obesity.[1] Metabolic syndrome, as an entity is controversial but its diagnosis indicates an increased relative risk of diabetes and cardiovascular events.[2] The identification of risk-factor clustering, which is a real and relatively common phenomenon, emphasizes the need to treat more aggressively those patients with multiple abnormalities, even though individually these abnormalities may be slight.[3] Epidemiological studies have demonstrated the increased prevalence of these abnormalities as a cluster than would be expected if they were together by chance.[1] The MetS provides an early, simple and inexpensive signal of an increased risk of cardiovascular disease and diabetes.

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease with an increased prevalence of atherosclerosis. Accelerated

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atherosclerosis and premature cardiovascular events have been recognized as an important cause of morbidity and mortality in lupus patients.[4–6] The mechanisms underlying the accelerated atherosclerosis in SLE are not fully understood. Lupus patients have an increased prevalence of traditional cardiovascular risk factors for coronary heart disease (CHD).[7–10] However, even after adjustment for Framingham risk factors, the risk for cardiovascular events is still increased,[5] suggesting the existence of additional factors including lupus characteristics.[11]

MetS is associated with inflammation which is characterized by increased circulation adipocytokines such as tumor necrosis factor-α (TNF-α), interleukin-6, leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), and acute-phase reactants such as C-reactive protein.[12–14] Inflammation may facilitate insulin resistance and impairs endothelium-dependent vasodilatation.[15] Interestingly, high levels of C-reactive protein predicted the presence of MetS in middle-aged men, even after adjustment for baseline cardiovascular risk factors and body mass index.[16] Lupus patients have higher plasma leptin, TNF-α levels, fibrinogen and PAI-1 levels than health controls.[17,18] They also present with high triglycerides and low HDL-cholesterol levels as the most frequent lipid profile abnormality, these levels are aggravated by disease activity.[19] All these abnormalities together link SLE to the metabolic derangements found in MetS patients that can, in turn, be associated with the increased risk of cardiovascular events in lupus patients.

The present study investigates the prevalence of metabolic syndrome and its determinants as well as the association of the syndrome with lupus characteristics and the traditional risk factors for CHD not included in the syndrome definition. The hypothesis of an association of MetS with lupus characteristics, independent of the traditional cardiovascular risk factors, is evaluated.

Patients and methods

This study has been approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais, Brazil.

Patients

From May 2005 to February 2006, 183 female lupus patients, 18 years of age or older, were invited to participate in a cross-sectional study of cardiovascular disease. All of them fulfilled the ACR lupus classification criteria.[20] Twenty-one patients were excluded from the initial study because they did not complete the protocol. The final group of 162 female patients evaluated in this study did not differ from the 148 patients of the Rheumatology Service database who have not been included in the study, except for a higher frequency of antinuclear antibody.

Protocol and definitions

Patients were evaluated using standardized clinical interview, physical examination, and laboratory tests in addition to chart reviews. Patients were classified as having MetS based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII), modified to include patients being treated for the abnormalities.[21,22] The NCEP/ATPIII defines the MetS as being present if three or more of the following five criteria are met: central obesity (waist circumference >88 cm in women); hypertriglyceridemia (triglycerides ≥150 mg/dl); low HDL-cholesterol <50 mg/dl in women; high blood pressure ≥130/85 mmHg; and fasting glucose ≥110 mg/dl. Changing the fasting glucose level to >100 mg/dl did not modified the results of this analysis.[22]

Lupus characteristics were collected. Systemic lupus cumulative damage was measured using the SLICC/ACR damage index.[23] Lupus activity was analyzed using the SLEDAI-2k, modified to exclude the serologic items (anti-DNA antibody and complement level).[24] Prednisone regimen data were registered considering: current dose (mg/day); maximum follow-up dose (mg/day); duration of use; cumulative dose during follow-up (g); and the average daily dose over follow-up (mg/day).

Other traditional risk factors for coronary artery disease not included in the syndrome definition were recorded: age; family history of coronary disease in a first-degree relative (men <55 years and women <65 years); obesity (BMI >30 kg/m^2); postmenopausal status and premature ovarian failure (age <40 years); smoking habit; total cholesterol ≥200 mg/dl; LDL-cholesterol ≥130 mg/dl and ≥100 mg/dl; and Framingham risk score as previously defined.[11,25]

Statistic

Continuous data were expressed as either mean (SD) or median (interquartile range), whereas categorical variables were expressed as numbers (percentages). Comparisons between patients with and without metabolic syndrome were made using Student's *t*-test and the Mann–Whitney test for continuous variables or Pearson's chi-squared test

Table 1 Metabolic syndrome variables in female patients with systemic lupus erythematosus

Metabolic syndrome variables	*Total patients (n = 162)*	*With metabolic syndrome (n = 52)*	*Without metabolic syndrome (n = 110)*	*p-value*[a]	*OR (95% CI)*
Metabolic syndrome	52 (32.1%)	52 (100%)	0 (0)	–	–
Waist circumference >88 cm	73 (45.1%)	45 (86.5%)	28 (25.5%)	<0.001	18.83 (7.62–46.52)
HDL <50 mg/dl[b]	99 (61.1%)	44 (84.6%)	55 (50.0%)	<0.001	5.50 (2.37–12.75)
Triglycerides ≥150 mg/dl[b]	47 (29.0%)	36 (69.2%)	11 (10.0%)	<0.001	20.25 (8.59–47.72)
SBP/DBP ≥130/85 mmHg[b]	93 (57.4%)	45 (86.5%)	48 (43.6%)	<0.001	8.30 (3.44–20.04)
Fasting glucose ≥110 mg/dl[b]	10 (6.2%)	9 (17.3%)	1 (0.9%)	<0.001	22.81 (2.81–185.54)

[a]Pearson's chi-squared test; [b]Or drug treatment for the risk factor.
Abbreviations: DBP, diastolic blood pressure; HDL, high density lipoprotein; SBP, systolic blood pressure.

and Fisher's exact test for categorical variables; univariate analysis.

To determine which factors were independently associated with MetS, the variables that presented $p < 0.10$ in the univariate analysis and those values with supposed clinical relevance or previous data in the literature were included in the multivariate logistic regression model.

Statistical analysis was performed using SPSS 12.0 for windows (SPSS Inc., Chicago, USA). A two-sided p-value <0.05 was considered significant.

Results

Study population

The mean (SD) age of the 162 lupus women studied was 38.8 (11.2) years. The median (interquartile range) disease and follow-up duration were 102.5 (54.0–159.0) months and 84.0 (52.0–136.0) months, respectively. The median (interquartile range) at SLE diagnosis was 27 (22–35) years. The median (interquartile range) damage index was 1 (0–3), maximum 7, and the modified SLEDAI-2k was 0 (0–4), maximum 18. No patient in the study presented renal disease requiring dialysis.

Metabolic syndrome

Fifty-two (32.1%; CI 95% = 24.9–39.3%) patients had MetS. Table 1 shows the frequency of the components of the MetS in the entire group studied and the frequency found in the patients with MetS. The most frequent risk factors in patients with MetS were abdominal obesity (86.5%) and high blood pressure (86.5%), followed by low HDL-cholesterol (84.6%), hypertriglyceridemia (69.2%), and hyperglycemia (15.4%). From the entire cohort, no patients were using drugs to treat hypertriglyceridemia, seven (4.3%) were using hypoglycemic drugs (five oral hypoglycemic drugs and two insulin), and 73 (45.1%) were taking antihypertensive medication.

The traditional risk factors for CHD not included in the syndrome definition and significantly associated with MetS were older age ($p = 0.001$), family history of early CHD ($p = 0.024$), postmenopausal status ($p = 0.026$) and premature ovarian failure ($p = 0.029$), high levels of total cholesterol ($p < 0.001$) and LDL-c ($p < 0.001$), obesity ($p < 0.001$), and higher Framingham risk score ($p < 0.001$) (Table 2).

Lupus characteristics associated with the syndrome were history of nephrotic proteinuria during lupus follow-up ($p = 0.008$), higher modified SLEDAI-2k ($p = 0.037$) and damage index (SLICC/ACR) ($p < 0.001$) and older age at SLE diagnosis ($p < 0.001$) (Table 3). The median (interquartile range) time between the first and the last nephrotic proteinuria to the metabolic syndrome diagnosis (the day of the study visit) were 48.9 (25.2–74.1) months and 32.8 (15.9–67.6) months, respectively. The current use of intravenous cyclophosphamide was the only treatment variable associated to MetS [11 patients (21.2%) with MetS versus 10 patients (9.1%) without MetS; $p = 0.045$]. No association was found between prednisone use and dosage with MetS.

The logistic regression analysis of 162 female patients included the following variables: age, family history for early coronary disease, obesity, LDL-cholesterol ≥100 mg/dl, postmenopausal status, nephrotic range proteinuria during follow-up, cyclophosphamide use, modified SLEDAI-2k, damage index (SLICC/ACR), and age at lupus diagnosis. In this logistic regression model, LDL-c ≥100 mg/dl ($p = 0.007$) and obesity ($p < 0.001$) were the two traditional risk factors independently associated with MetS in these lupus patients. A history of lupus nephritis with nephrotic range proteinuria ($p = 0.025$), higher damage index score ($p = 0.006$), and an older age at lupus diagnosis ($p = 0.007$) were associated with the present diagnosis of MetS independent of the traditional risk factors for CHD (Table 4). The logistic regression analysis using a modified damage index

Table 2 Association between traditional coronary risk factors and metabolic syndrome in female lupus patients, univariate analysis

Traditional risk factors	*Total (n = 162)*	*With metabolic syndrome (n = 52)*	*Without metabolic syndrome (n = 110)*	*p-value*[a]	*OR (CI 95%)*
Age (years)[b]	38.8 (11.2)	43.4 (10.9)	36.6 (10.7)	0.001	–
FH	22 (13.8)	12 (23.5)	10 (9.2)	0.024	3.05 (1.22–7.63)
Obesity	35 (21.6)	26 (50.0)	9 (8.2)	<0.001	11.22 (4.69–26.84)
Postmenopausal status	66 (40.7)	28 (53.8)	38 (34.5)	0.026	2.21 (1.13–4.33)
Premature ovarian failure	28 (17.3)	14 (26.9)	14 (12.7)	0.029	2.53 (1.10–5.80)
Smoking	22 (13.6)	6 (11.5)	16 (14.5)	0.636	0.77 (0.28–2.09)
Total cholesterol ≥200 mg/dl	32 (19.8)	22 (42.3)	10 (9.1)	<0.001	7.33 (3.13–17.19)
LDL-c ≥130 mg/dl	30 (18.5)	20 (38.5)	10 (9.1)	<0.001	6.25 (2.65–14.73)
LDL-c ≥100 mg/dl	73 (45.1)	34 (65.4)	39 (35.5)	<0.001	3.44 (1.72–6.87)
Framingham risk score[c]	1 (1–4)	2.5 (1–8)	1 (1–3)	<0.001	–

Data were expressed as number (%) except when indicated.
[a]Pearson chi-squared test, Fisher's exact test, Mann–Whitney test, Student's *t*-test as appropriated; [b]mean (SD); [c]median (interquartile range).
Abbreviations: FH, family history of coronary heart disease; LDL-c, low density lipoprotein cholesterol.

Table 3 Association between lupus characteristics and metabolic syndrome in female lupus patients, univariate analysis

Lupus-related characteristics during disease follow-up	*Total (n = 162)*	*With metabolic syndrome (n = 52)*	*Without metabolic syndrome (n = 110)*	*p-value*[a]	*OR (CI 95%)*
Mucocutaneous manifestations	132 (81.5)	44 (84.6)	88 (80)	0.525	1.38 (0.57–3.34)
Arthritis	104 (64.2)	32 (61.5)	72 (65.5)	0.726	0.84 (0.43–1.67)
Serositis	50 (30.9)	16 (30.8)	34 (30.9)	1.000	0.99 (0.49–2.03)
Nephritis	57 (59.9)	34 (65.4)	63 (57.3)	0.392	1.41 (0.71–2.80)
Nephrotic proteinuria (follow-up)	35 (21.6)	18 (34.6)	17 (15.5)	0.008	2.90 (1.34–6.26)
Nephrotic proteinuria (current)	4 (2.5)	3 (5.8)	1 (0.9)	0.098	6.67 (0.68–65.78)
Neuropsychiatric disorders	25 (15.4)	8 (15.4)	17 (15.5)	1.000	0.99 (0.40–2.48)
Hematologic abnormalities	144 (88.9)	47 (90.4)	97 (88.2)	0.793	1.26 (0.42–3.74)
Hemolytic anemia	27 (16.7)	7 (13.5)	20 (18.2)	0.507	0.7 (0.28–1.78)
Leuko-/lymphopenia	141 (87)	44 (88.5)	95 (86.4)	0.806	1.21 (0.44–3.32)
Thrombocytopenia	24 (14.8)	6 (11.5)	18 (16.4)	0.485	0.67 (0.25–1.79)
Positive ANA	162 (100)	52 (100)	110 (52)	–	–
Antibody to dsDNA[c]	76 (47.2)	21 (40.4)	55 (50.5)	0.152	0.67 (0.34–1.30)
Antibody to Sm[e]	43 (27)	16 (31.4)	27 (25)	0.446	1.37 (0.66–2.86)
False positive VDRL[c]	13 (8.1)	5 (9.8)	8 (7.3)	0.757	1.39 (0.43–4.47)
Positive LA	22 (13.6)	6 (11.5)	16 (14.5)	0.636	0.77 (0.28–2.09)
Positive aCL[d]	38 (23.8)	13 (25.5)	25 (22.9)	0.842	1.15 (0.53–2.49)
Modified SLEDAI-2k[b]	0 (0–4)	2 (0–4)	0 (0–2)	0.037	–
Modified SLEDAI-2k > 4	48 (29.6)	22 (42.3)	26 (23.6)	0.018	2.37 (1.17–4.79)
Damage Index (SLICC/ACR)[b]	1 (0–3)	2 (1–4)	1 (0–2)	<0.001	–
Age at diagnosis (years)[b]	27 (22–35)	30.5 (25–38.5)	25.5 (21.0–33.0)	0.001	–
Disease duration (months)[b]	102.5 (54–159)	104 (61.5–168)	100 (48–152)	0.311	–
Disease follow-up (months)[b]	84 (52–136)	91.5 (59–145)	75 (46–128)	0.129	–

Data expressed as number (%) except when indicated. [a]Pearson chi-squared test, Fisher's exact test, Mann–Whitney test, Student's *t*-test as appropriated; [b]median (interquartile range); [c]Not done in one patient; [d]Not done in two patients; [e]Not done in three patients.

score excluding conditions possibly associated with atherosclerosis (angina and coronary bypass, myocardial infarction, stroke and claudication) did not change the final model (data not shown).

Discussion

In this study 52 (32.1%) lupus patients presented with metabolic syndrome (MetS) according to the modified NCEP/ATPIII criteria. This frequency is higher than the one described by Azevedo *et al*. in another set of Brazilian lupus patients (20.0%).[26] Those authors excluded patients with diabetes and nephrotic syndrome from their analysis, which could explain this difference.

The frequency of MetS found in our study is also higher than the frequency found in lupus patients in Mexico (16.7%),[27] in Argentina (28.6%),[28] in The Netherlands (16%),[29] and also in the USA

Table 4 Association between traditional risk factors and lupus characteristics and metabolic syndrome in 162 female lupus patients, logistic regression analysis

Variables	*B*	*OR*	*CI (95%)*	*p-value*
Obesity	2.669	14.430	4.905–42.450	<0.001
LDL-cholesterol ≥100 mg/dl	1.254	3.504	1.418–8.662	0.007
Nephrotic proteinuria (follow-up)	1.214	3.368	1.165–9.733	0.025
Damage Index (SLICC/ACR)	0.353	1.424	1.107–1.831	0.006
Age at lupus diagnosis	0.063	1.065	1.017–1.114	0.007

Adjusted for age, family history for early coronary disease, postmenopausal status, disease activity (modified SLEDAI-2k), current cyclophosphamide use.
Classification table: percentage correct with MetS = 65.4, without MetS = 90.0, overall = 82.7. Cox and Snell $r^2 = 0.349$; Nagelkerke $r^2 = 0.488$.
Abbreviations: B, backward stepwise; OR, overall model fit: omnibus chi-squared test = 69.578; df = 5, $p < 0.001$.

(29.4%),[15] even though these patients had very similar mean ages: 37 years, 37.2 years, 39 years, and 40 years, respectively. Negron *et al*. studied MetS in 204 lupus patients in Puerto Rico, mean (SD) age at study visit 43.6 years, [14] and diagnosed the syndrome in 78 (38.2%) patients. It is important to note that social class is associated with the prevalence of all the five risk factors that define the syndrome and it has already been observed that the prevalence of MetS is higher among the poorest.[14,27,30] In female lupus patients, MetS has been associated with lower income and government health insurance.[14,27] This finding could explain the lower frequency of MetS found in the USA and The Netherlands compared with Puerto Rico and Brazil. Also, susceptibility factors to the syndrome include adipose tissue disorder (typically manifested as abdominal obesity), genetic and racial factors, aging, endocrine disorders, lifestyle, and diet habits.[3] Altogether, these factors could contribute to the differences found in MetS frequency among all mentioned studies.

Patients with MetS carry a higher risk of atherosclerosis and diabetes. Analysis from the Framingham Offspring Cohort showed age-adjusted relative risk for cardiovascular disease, coronary heart disease and type 2 diabetes of 2.1, 1.5 and 6.9 for women,[1] respectively. Moreover, Girman *et al*. showed that the increased event rate in subjects with MetS remained significant after adjustment for the Framingham 10-year risk, suggesting that the syndrome carries an additional risk not captured by the Framingham risk scoring.[31] Even more, in the European DECODE study,[32] in men at low risk (estimated 10-year risk of cardiovascular mortality under 5%) MetS had a relative risk of cardiovascular mortality of 2.5 (1.2–5.0). For women there were fewer cardiovascular events and the diagnosis of MetS had no statistical association with cardiovascular death. This observation may be important, especially in lupus women, as the frequency of cardiovascular events is far higher than that of the general female population, even though the Framingham risk score is low in most of them.[15] Again, the Framingham risk scoring model does not adequately predict the risk of clinical[5] and subclinical[33] atherosclerosis in lupus patients and the use of MetS concept can help to better classify those women as at risk for cardiovascular disease. Whether MetS will have predictive value in these patients has to be elucidated.

We found that, beyond the clustering of the risk factor that comprises the syndrome, MetS is also associated with other traditional risk factors for CHD, mainly obesity and LDL-c ≥100 mg/dl. The latter is especially important as this is the target level that has been proposed for lupus patients and it is associated with subclinical atherosclerosis in these patients.[11, 25] These findings reinforce the idea of risk factor clustering in lupus patients and health professionals who take care of these patients should be aware of this fact.

We found no association of prednisone use and MetS, in accordance with other authors.[15,27] It is well known that glucocorticoids have deleterious side effects with regards to cardiovascular risk and MetS components. Glucocorticoids promote hypertriglyceridemia and insulin resistance and are associated with a higher cholesterol plasma level, higher blood pressure and weight change in lupus patients.[34,35] The use of prednisone >10 mg/day and intravenous methylprednisolone has been previously associated to MetS diagnosis and components in lupus patients.[14,29] However, higher doses of prednisone and intravenous methylprednisolone could be reflective of disease activity and lupus severity.[14,35] As steroids are employed for their anti-inflammatory properties in SLE they may in part be beneficial, making this issue complex and unresolved.[17]

It is well known that the nephrotic syndrome is characterized by dyslipidemia and, in lupus patients, it is associated with more severe disease and inflammatory activity. The patients with severe nephritis are frequently treated with high-dose prednisone, or its equivalent, and intravenous cyclophosphamide. Thus, the association found in univariate analysis of intravenous cyclophosphamide use and MetS could be just a result of the association of nephrotic proteinuria with MetS.

In fact, in the logistic model, the history of proteinuria ≥3.5 g/24 h was a stronger and independently variable associated to MetS. It is interesting to note that nephrotic proteinuria is associated with MetS even after the patients failed to present nephrotic proteinuria (Table 3). This investigation is a cross-sectional study and no inferences about causality can be made, although our data suggest that we should pay special attention to patients with severe lupus nephritis regarding MetS.

The severity and persistence of lupus activity and its treatment are important determinants of lupus damage measured by SLICC/ACR damage index (SDI). As MetS could be influenced by these same factors, the association of MetS and SDI found in the present study and in the study by Bellomio *et al.* is not surprising.[28] If the diagnosis of MetS is to have a prognostic value, as the SDI has, is a matter for future prospective studies.

Our study has some limitations. First, as cited above, this investigation was a cross-sectional study and to answer some of the questions we may need a prospective study. Second, due to the lack of a control group we could not investigate if lupus itself is related to the high frequency of MetS found in our study. Finally, only one definition of MetS was used, the NCEP/ATPIII one, modified to include treatment. In the literature we can find several definitions for MetS. The differences between these are essentially the thresholds for the parameters to define a syndrome abnormality, the number of abnormalities before the syndrome is deemed present, and whether there is a compulsory abnormality that is required to be present. Reaven's arguments were centered on insulin resistance, and the definitions proposed by the World Health Organization (WHO), the International Diabetes Federation (IDF) and the European Group for the study of Insulin resistance (EGIR) have taken this situation into account.[36] Unfortunately, we did not measure plasma insulin (one of the requirements for the WHO definition) and we chose the most frequently used definition in lupus studies. It is obvious that different definitions may lead to different frequencies of the syndrome. However, Chung *et al.* defined MetS in lupus patients using the WHO and the NCEP/ATPIII definitions and found a very similar frequency of the syndrome (44.1% and 48.0%, respectively).[15] The most recent diagnostic criteria proposed by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) in 2005,[22] included the treatment for the abnormalities (which we used) and the lower threshold for fasting glucose (>100 mg/dl), which did not change the frequency of MetS in our patients (data not shown).

In summary, this study showed that female lupus patients have a high frequency of MetS. The syndrome was associated not only with traditional risk factors, confirming the clustering of risk factors for CHD, but also with lupus characteristics. The predictive value of cardiovascular events and diabetes mellitus of MetS in SLE has yet to be demonstrated.

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