Prevalence of and risk factors for the metabolic syndrome in women with systemic lupus erythematosus

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Abstract

Objective

To examine the prevalence of the metabolic syndrome and the relationship between metabolic syndrome score (MetS score) and disease characteristics and cardiovascular events (CVEs) in women with SLE.

Methods

Demographic and clinical data were collected in 141 female SLE patients. The prevalence of the metabolic syndrome was defined by a modified National Cholesterol Education Program (NCEP/ATP III) definition. Metabolic syndrome was defined as MetS score ≥ 3.

Results

Twenty-three (16%) of the 141 SLE patients (mean age 39 ± 12 years, mean disease duration 6.2 ± 6.6 years) fulfilled the criteria of the metabolic syndrome. The mean MetS score was significantly higher in patients with SLE and a history of cardiovascular events (CVEs) than in those without a previous CVE. In linear multiple regression analysis, a high MetS score was significantly associated with previous intravenous methylprednisolone use, older age, higher ESR, higher C3 levels and higher serum creatinine levels.

Conclusions

In our female SLE patients, a high prevalence of the metabolic syndrome was found as compared to healthy women in the Amsterdam Growth and Health Longitudinal Study. Independent risk factors for high MetS score in patients with SLE are previous treatment with intravenous methylprednisolone, renal insufficiency, older age, higher ESR and higher C3 levels. These results suggest that assessment of the metabolic syndrome in patients with SLE might be important to identify subgroups of patients that are at disproportional high risk of developing cardiovascular disease and diabetes mellitus.

Key words

Metabolic syndrome, systemic lupus erythematosus, cardiovascular disease.

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Reprints will not be available from the author.

Received on December 20, 2006; accepted in revised form on July 3, 2007.

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Competing interests: none declared.

Introduction

Over the last few decades, accelerated atherosclerosis and premature cardiovascular disease, including coronary heart disease, ischaemic cerebrovascular disease, and peripheral vascular disease, have been recognized as an important cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) (1-3). The incidence of myocardial infarction is five times higher in patients with SLE as compared with the general population (2). Several studies of surrogate markers have also demonstrated a high prevalence of subclinical atherosclerosis in patients with SLE (4, 5). The mechanisms underlying the accelerated atherosclerosis in SLE are not fully understood. Patients with SLE have an increased prevalence of several traditional risk factors for atherosclerosis, such as hypertension and diabetes mellitus (6). However, even after adjustment for the presence of the traditional Framingham risk factors, the risk for cardiovascular events in patients with SLE is still 7 to 17-fold increased (7). Therefore, additional metabolic, inflammatory and lifestyle factors are suggested to contribute to the development of atherosclerosis in SLE.

The metabolic syndrome is a condition characterized by the clustering of cardiovascular risk factors, including hypertension, obesity, impaired glucose tolerance and dyslipidaemia, and is associated with an increased risk of diabetes mellitus and cardiovascular morbidity and mortality in the general population, especially in women (8, 9). Assessment of the metabolic syndrome may have surplus value above the assessment of the Framingham risk score. The Framingham risk score predicts development only of cardiovascular disease whereas the presence of the metabolic syndrome predicts both diabetes and cardiovascular disease. The reported prevalence of the metabolic syndrome in the general population in developed countries varies between 3 and 43%, depending on the definition used, age, gender and ethnicity (10, 11). In healthy young women in the Netherlands, the prevalence of the metabolic syndrome is 3.2%, as reported in the Amsterdam Growth and Health Longitudinal Study (10). Data on the prevalence of and risk factors for the metabolic syndrome in SLE are scarce. A recent study in the United Kingdom reported that 18% of 61 female SLE patients, as compared with 2.5% of healthy female controls, fulfilled the criteria of the NCEP metabolic syndrome (12). Awareness of the metabolic syndrome in the already high-risk population of patients with SLE may help to identify a subgroup of patients with multiple factors that confer an even higher risk for future cardiovascular events and diabetes mellitus and may require preventive measures.

The aim of the present study was to investigate the prevalence of the metabolic syndrome and its determinants as well as to study the relation between the (components of the) MetS score and disease characteristics and cardiovascular events in a large population of women with SLE.

Materials and methods

Patients

One hundred and forty-one consecutive female patients fulfilling the ACR revised criteria for the classification of SLE were included in the study (13). All patients regularly attended the outpatient rheumatology clinic of either the VU University Medical Center, the Jan van Breemen Institute or the Slotervaart Hospital. These institutes provide primary through tertiary care for SLE patients in Amsterdam, The Netherlands. All patients provided informed consent for their participation. The local ethics committee approved the study.

Data collection and clinical measures

Demographic and clinical characteristics were systematically recorded by interview, self-reported questionnaires, chart review and clinical examination, performed by two rheumatologists (IB, FT). The following data were collected at the time of study inclusion:

A. Historic variables

a. Risk factors for CVD: Data collection comprised tobacco intake and documented previous arterial cardiovascular events (CVEs). Coronary artery events were defined as myocardial

infarction, coronary artery by-pass surgery, coronary angioplasty/stenting, and angina pectoris. Ischaemic cerebrovascular events were defined as transient ischaemic attacks, ischaemic stroke, or carotid endarterectomy. Peripheral artery events were defined as peripheral grafting or symptomatic peripheral artery ischaemia, confirmed by angiography.
b. SLE related factors included: history of biopsy proven lupus nephritis.
c. Treatment: History of corticosteroid use, including past intravenous (IV) methylprednisolone use and oral corticosteroid use (past use, duration of use in months, maximum dosage ever taken), was documented. Past use of antirheumatic drugs, anti-hypertensive medication, anti-diabetic medication, anticoagulants and lipid lowering agents were also documented.

B. Variables at the time of the evaluation

These included age, disease duration, race, menstrual status, tobacco intake and exercise status. Exercise was defined as the weekly frequency of ≥ 40 minutes of aerobic exercise performed. Current use of corticosteroids, including IV methylprednisolone and oral corticosteroids (current use, actual dosage). Current use of antirheumatic drugs, anti-hypertensive medication, anti-diabetic medication, anticoagulants and lipid lowering agents.
All patients were studied following an overnight fast. Body weight, height, body mass index (BMI) and blood pressure were assessed. Brachial pulse pressure was defined as systolic minus diastolic blood pressure (14, 15). Disease activity was scored using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the European Consensus Lupus Activity Measure (ECLAM) (16, 17). Accumulated organ damage was assessed with the SLICC/ACR damage index (DI) (18). A modified DI score was derived as the DI score excluding cardiovascular events, diabetes mellitus and renal complications as damage items.
Laboratory investigations at the time of the study inclusion were: clinical biochemistry profile (including C reactive protein (CRP), serum creatinine, fasting levels of plasma glucose, plasma homocysteine, serum total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides (TG)), antiphospholipid antibodies and anti-dsDNA titres. Serum levels of C3 and C4 were measured by nephelometry (Immage Immunochemistry Systems, Beckman Coulter, Fullerton, USA).

C. Metabolic syndrome definition

To identify the metabolic syndrome, we used a modified version of the definition employed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (19). The metabolic syndrome was ascertained when 3 or more of the following 5 risk factors were present: fasting plasma glucose ≥ 6.1 mmol/l and/or use of blood glucose lowering medication, elevated blood pressure ≥ 130 mmHg systolic and/or ≥ 85 mmHg diastolic and/or antihypertensive therapy, serum TG levels of ≥ 1.7 mmol/l, HDL-C levels < 1.29 mmol/l and finally BMI ≥ 30 kg/m^2. This last measure was chosen since waist circumference data were not available in our data set. The metabolic syndrome score (MetS score) is defined as the total number of components of the metabolic syndrome present in a single patient.

Statistical analysis

MetS score in patients with SLE with and without a history of previous CVEs were compared using the non-parametric (Mann-Whitney) test. Associations between MetS score and clinical and biochemical variables were identified by univariate tests and subsequently by multiple regression analyses. The following variables were examined in relationship to metabolic syndrome score by univariate analyses: age, race, menstrual status, smoking, exercise, disease duration, disease activity, modified DI score, serum creatinine, acute phase parameters, presence of anti-phospholipid antibodies, anti-dsDNA, complement C3 and C4 levels, history of lupus nephritis confirmed by renal biopsy, previous and current use of the following drugs: IV methylprednisolone, oral corticosteroids, hydroxychloroquine, azathioprine, methotrexate, (oral and/or intravenous) cyclophosphamide. To determine which factors were significantly associated with the MetS score, the demographic, clinical and therapy variables with $p < 0.2$ in the univariate analyses and variables with supposed clinical relevance were entered into the respective multiple regression analyses. The stability of the model was checked by tentatively adding to the (almost) final model single variables initially not included in the model, so as to check once more whether these variables could indeed be missed.
Statistical analysis was performed using SPSS 13.0 for windows (SPSS Inc, Chicago, USA). A two-sided value of $p < 0.05$ was considered statistically significant.

Results

Demographic, clinical and treatment variables

The demographic, clinical and therapy characteristics of the 141 female SLE patients included in the study are shown in Table I.
The majority of the patients were young, Caucasian patients with a mean disease duration of 6 years. The ethnic background of the remaining 30% of patients was: Asiatic (12%), Negroid (8%), Mediterranean (4%) and other (6%). At the time of inclusion most patients had mild disease activity. Fifty-two percent of the patients had organ damage (unmodified DI ≥ 1). Most patients had used oral corticosteroids and hydroxychloroquine in the past and a large number of patients had been treated with IV methylprednisolone. At least one previous arterial CVE was documented in 16/141 (11%) patients. Coronary artery events had occurred in seven (5%), ischaemic cerebrovascular events in ten (7%), and peripheral artery disease was documented in three patients (2%).

Metabolic syndrome

The metabolic syndrome was present in 16% of the patients. One hundred and six (75%) patients had ≥ 1 metabolic syndrome risk factor and the mean MetS score was 1.4 ± 1.2 (mean ± SD). Figure 1 shows the distribution of the

Table I. Demographic, clinical and therapy variables.

1A. Historic variables	All patients (n = 141)
Clinical variables	
Lupus nephritis ever, %	23.4
Previous CVE, %	11.3
Therapy variables	
Oral corticosteroids	
– Ever user, %	82
– Treatment duration in ever users, months	52 ± 61
Ever use of other medications, %	
– IV Methylprednisolone, %	23
– Hydroxychloroquine, %	84
– Cyclophosphamide, %	12
– Azathioprine, %	38
– Anti-hypertensive therapy, %	37
Potential risk factors for arterial cardiovascular disease	
Ever smoker, %	50
1B. Current variables	
Demographic variables	
Age, years	39 ± 12
Caucasian race, %	70
Premenopausal, %	72
Clinical variables	
Disease duration, years	6.2 ± 6.6
SLEDAI	4.7 ± 3.6
ECLAM	3.1 ± 1.6
SLICC/ACR damage index	1.2 ± 1.8
SLICC/ACR damage index modified	0.8 ± 1.3
Systolic BP, mmHg	130 ± 18
Diastolic BP, mmHg	79 ± 10
Pulse pressure	51 ± 12
ESR, mm/1st h	24 ± 16
CRP, mg/l	9 ± 5
Fasting glucose, mmol/l	5 ± 0.8
Serum creatinine, μmol/l	85 ± 19
Complement C3, g/l	0.88 ± 0.29
Complement C3 below reference value (0.88 g/l), %	55
Complement C4, g/l	0.15 ± 0.06
Complement C4 below reference value (0.16 g/l), %	64
Anti-dsDNA, IE/ml	29 ± 55
Anti-dsDNA > 0 IE/ml, %	43
Therapy variables	
Oral corticosteroids	
– Current user, %	56
– Actual daily prednisone dose total group, mg	7 ± 10
– Actual daily prednisone dose if > 0 mg/day, mg	13 ± 11
Current use of other medications, %	
– IV Methylprednisolone, %	1
– Hydroxychloroquine, %	49
– Cyclophosphamide, %	4
– Azathioprine, %	18
– Anti-hypertensive therapy, %	31
Potential risk factors for arterial cardiovascular disease	
BMI, kg/m^2	25 ± 6
Current smoker, %	22
Exercise ≥ 3 times weekly, %	27
Serum HDL cholesterol, mmol/l	1.5 ± 0.4
Serum triglycerides, mmol/l	1.3 ± 0.7
Serum homocysteine, μmol/l	11.5 ± 5.4

Except where indicated otherwise, values are the mean ± SD.
CVE: arterial cardiovascular event; IV: intravenous; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index (range 0-105); ECLAM: European Consensus Lupus Activity Measurement (range 0-10); SLICC/ACR damage index: Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLICC/ACR damage modified: damage index score excluding cardiovascular events, diabetes and renal complications as damage items; BP: blood pressure; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index; HDL: high density lipoprotein.

MetS score in the study population. Hypertension was the most frequent risk factor, which was present in 84 (60%) of the patients. Decreased HDL-C levels were present in 45 (32%) and elevated TG levels in 32 (23%) patients. Obesity, defined as BMI ≥ 30 kg/m^2, was found in 19 (14%) of the patients. Sixteen (11%) patients had fasting plasma glucose levels ≥ 6.1 mmol/l and/or used blood glucose lowering agents.

Variables associated with MetS score

Table II shows the results of univariate analyses. In a stepwise multiple regression analysis high MetS score was significantly, independently and positively associated with previous IV methylprednisolone use, age, ESR, high C3 levels and serum creatinine (Table III). None of the other variables investigated demonstrated a significant contribution to the model.

Association between metabolic syndrome score and previous CVE

The MetS score (2.06 ± 1.28 [mean ± SD]) in patients with SLE and a history of CVE was significantly higher than in patients with SLE without a history of CVE (1.30 ± 1.05, $p = 0.027$).

Association between metabolic syndrome score and pulse pressure

Forty-three (31%) patients with SLE had a high pulse pressure (≥ 60 mmHg). MetS score was significantly associated with pulse pressure ($p = 0.003$), even after correction for age and serum creatinine level.

Discussion

In this study we found a high prevalence (16%) of the metabolic syndrome in a cohort of young women with SLE in comparison to the 3.2% frequency found in healthy young women in the Amsterdam Growth and Health Longitudinal Study in The Netherlands (10). A high MetS score was significantly associated with previous IV methylprednisolone use, renal insufficiency and some markers of inflammation. In addition, high MetS score was significantly associated with CVEs and with high pulse pressure. This is the first study showing an association between

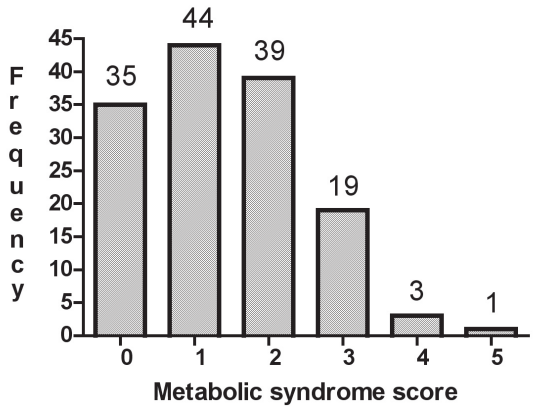

Fig. 1. Distribution of the metabolic syndrome score in female patients with SLE.
Metabolic syndrome score (MetS score) in 141 female patients with SLE.
Bars represent the absolute numbers of SLE patients with a specific MetS score.

Table II. Univariate analyses of variables possibly associated with metabolic syndrome score.

Variables	B	95% CI	*p* value
Age at inclusion (years)	0.025	0.010 to 0.040	0.001
Postmenopausal status	0.717	0.297 to 1.137	0.001
Caucasian race	0.047	-0.358 to 0.451	0.819
Current smoking	0.053	-0.181 to 0.287	0.654
Exercise (weekly frequency)	-0.052	-0.215 to 0.111	0.529
Disease duration (years)	0.022	-0.006 to 0.050	0.127
History of lupus nephritis	0.598	0.173 to 1.024	0.006
ESR (mm/1 st h)	0.014	0.006 to 0.021	0.001
CRP (mg/l)	0.018	0.001 to 0.035	0.038
Serum creatinine (µmol/l)	0.015	0.006 to 0.024	0.002
Complement C3 (g/l)	0.914	0.300 to 1.528	0.004
Complement C4 (g/l)	2.202	-0.682 to 5.087	0.133
Titre of anti-dsDNA (IE/ml)	-0.001	-0.004 to 0.003	0.696
SLEDAI	0.018	-0.034 to 0.070	0.493
ECLAM	0.054	-0.060 to 0.169	0.350
SDI (modified)	0.192	0.054 to 0.331	0.007
Current hydroxychloroquine use	-0.395	-0.759 to -0.031	0.034
Hydroxychloroquine use ever	-0.365	-0.862 to 0.132	0.148
Current oral corticosteroid use	0.178	-0.193 to 0.550	0.345
Duration of oral corticosteroid use (months)	0.003	0.000 to 0.006	0.075
IV methylprednisolone use ever	0.627	0.198 to 1.056	0.004
IV cyclophosphamide use ever	0.677	0.069 to 1.285	0.029
Current azathioprine use	0.088	-0.389 to 0.564	0.717
Azathioprine use ever	0.478	0.106 to 0.850	0.012

B: regression coefficient; 95% CI: 95% confidence interval; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ECLAM: European Consensus Lupus Activity Measurement; SDI: Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index; IV: intravenous.

MetS score and disease characteristics and CVEs in patients with SLE.

The increased frequency of the metabolic syndrome found in our population is consistent with a recent study demonstrating prevalence of the metabolic syndrome in 18% of 61 female SLE patients with mean age 48 years in the United Kingdom (12). Moreover, the high frequency of hypertension, dyslipidaemia and diabetes demonstrated in our subjects, is confirmed by previous studies (12, 20, 21). Obesity was present in only 14% of our patients as compared to a 28-39% reported obesity frequency in other studies in patients with SLE in Europe, the United States and Canada (6, 20, 22-24). This finding might be explained by a low background prevalence of obesity in The Netherlands. Therefore, we hypothesize that the prevalence of the metabolic syndrome may be even higher among SLE patients in populations with a higher prevalence of obesity in the general population.

Interestingly, an association between high C3 levels and high MetS score was found in the present study. In two previous studies in patients with SLE, an association between high C3 levels and vascular stiffness of the aorta and with coronary artery calcification and symptomatic coronary heart disease was demonstrated (21, 23). Moreover, studies in the general population have demonstrated associations between high C3 levels and traditional cardiovascular risk factors and coronary heart disease (25, 26). In some, but not all studies in SLE, low C3 levels have been detected in patients with active disease (27). However, during the acute phase response of inflammation, C3 synthesis may increase and this increase may outweigh breakdown of C3 during activation (27, 28). Another explanation for the association found between high C3 levels and high MetS score might be increased hepatic production of C3 in obese patients. Adipocyte-derived cytokines, such as TNF-α and IL-1, stimulate hepatic production of C3 (25). High serum C3 levels are associated with obesity in the general population (29). In women with SLE we found increasing C3 levels with increasing BMI (Fig. 2) which supports our hypothesis that increased hepatic production of C3, mediated by adipocyte-derived cytokines, may in part explain the association found between high C3 levels and high MetS score in our patients with SLE. Further studies are needed to confirm this hypothesis.

The association between higher serum creatinine levels and higher MetS score in our patients with SLE is consistent with results from studies in the general population demonstrating an increase in the number of cardiovascular risk factors with stage of kidney dysfunction (30). At study inclusion, more than 50% of the patients in our study had a calculated creatinine clearance < 90 ml/min. The high prevalence of impaired kidney function in our patients illustrates the importance of this risk factor in SLE.

Table III. Multivariate analysis of metabolic syndrome score (dependent variable), clinical and therapy variables (independent variables).

Variables	B	95% CI	Standardised B	*p* value
IV methylprednisolone use ever	0.759	0.367 to 1.152	0.288	< 0.001
Complement C3, g/l	0.845	0.270 to 1.420	0.224	< 0.01
Age at inclusion, years	0.020	0.006 to 0.034	0.220	< 0.01
ESR, mm/1 st h	0.010	0.002 to 0.017	0.201	< 0.01
Serum creatinine, μmol/l	0.009	0.000 to 0.018	0.154	0.045

B: regression coefficient; 95% CI: 95% confidence interval; IV: intravenous; ESR: erythrocyte sedimentation rate.

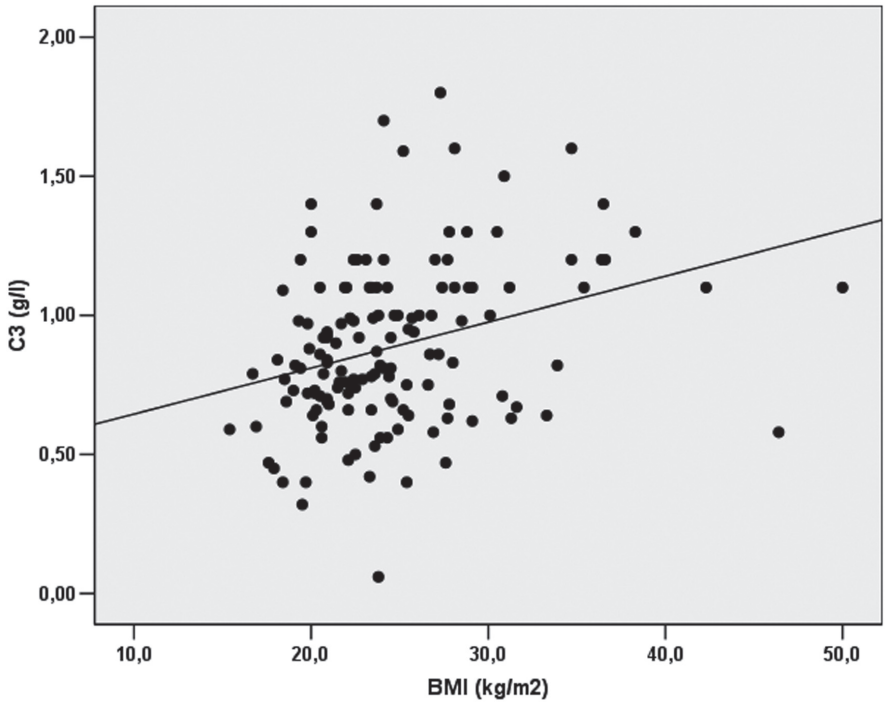

Fig. 2. Relationship between serum C3 levels and BMI in female patients with SLE.
Scatter plot showing the relationship between serum C3 levels and BMI in 141 women with SLE. Pearson correlation coefficient $r = 0.312$ ($p < 0.001$).

In our study, a significant association between previous IV methylprednisolone use and high MetS score was found. This finding is in contrast with the results of the United Kingdom study, which showed no association between current or recent corticosteroid dose and prevalence of the metabolic syndrome in a smaller group of patients with SLE. This discrepancy might be explained by differences in parameters of corticosteroid use evaluated between both studies and the larger size of our study population. Our results are in line with results of other studies demonstrating an association of corticosteroid use and an increased prevalence of hypertension, dyslipidaemia and obesity in patients with SLE (20, 31). Since IV methylprednisolone is used for severe complications of SLE, like nephritis and central nervous system involvement, patients with these disease complications might be at an increased risk for the development of multiple cardiovascular risk factors.

The finding that patients with SLE with a history of CVE had a significantly higher mean MetS score than SLE patients without previous CVEs is concordant with studies in the general population reporting a high frequency of the metabolic syndrome and an association between the metabolic syndrome and advanced vascular damage in patients with a history of CVEs (32, 33).

Brachial pulse pressure, an index of arterial stiffness, has been identified as an important predictor of myocardial infarction and cardiovascular mortality in the general population (14, 15). In our study, a third part of the SLE patients had a high pulse pressure (≥ 60 mmHg) and a significant association between high MetS score and high pulse pressure was demonstrated. A prospective study is needed to investigate whether also in patients with SLE high pulse pressure is a predictor of CVEs and cardiovascular mortality.

A limitation of the present study is the predominant presence of Caucasians in the study population which limits the generalization of its results to other lupus cohorts of different racial background.

The pathogenesis and definition of the metabolic syndrome are still under debate (34). Insulin resistance seems to be important in the pathogenesis of the metabolic syndrome, but also inflammation and oxidative stress are contributing factors (35, 36). Recently, increased insulin resistance in nondiabetic women with SLE in comparison to healthy controls was demonstrated (12). Both intensive lifestyle intervention (dietary modification, weight reduction and enhanced physical activity) and metformin therapy have been proven effective in the prevention and treatment of the metabolic syndrome in the general population (37). However, long-term lifestyle modifications may not be feasible in many subjects, and therefore pharmacological therapies are needed to lower CVD risk. Since no single pathogenic mechanism has been identified, prescription of pharmacological therapies targeting the individual components of the metabolic syndrome, in particular dyslipidaemia, hypertension and high glucose, may currently be the only therapeutic option.

In conclusion, the results of the present study demonstrate a high prevalence of the metabolic syndrome in women with SLE, a disease characterized by chronic inflammation, accelerated atherosclerosis and premature cardiovascular disease. Hypertension and dyslipidaemia, not obesity, were recognized as the most frequent components of the metabolic

syndrome in this patient population. Besides traditional cardiovascular risk factors, such as age, we were able to identify SLE related and treatment related factors associated with high MetS score. Based on these findings, subgroups of female lupus patients may be identified that are at disproportional high risk of developing cardiovascular disease and diabetes mellitus, with possibly therapeutic consequences.

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