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Abstract

Objective—Morbidity and mortality secondary to premature cardiovascular disease (CVD) in systemic lupus erythematosus (SLE) remain significant issues. The pathogenesis of CVD in SLE patients has not been fully explored. Epicardial adipose tissue (EAT) is believed to contribute to atherosclerosis development, through a paracrine and systemic inflammatory effect. We measured EAT volume in 162 SLE patients and 86 matched controls to assess the association of EAT with markers of atherosclerosis, cardiovascular risk and immunoactivation.

Methods—Clinical and laboratory characteristics collected included anthropomorphic measures, disease activity and damage indices, blood pressure measurement, lipid profile, inflammatory indices, adipokine levels and measures of adiposity. Coronary artery calcium (CAC) and EAT volume were measured using non-contrast cardiac computed tomography.

Results—EAT volume was greater in patients with SLE [(mean± SD) 96.8±45.9cm³] than controls (78.2±40.7 cm³; P=0.001). The EAT volume was 31% larger (95% CI, 16.5% – 47.4%) in SLE patients than controls (P<0.001 adjusted for age, sex, and race; after additional adjustment for waist circumference P=0.007). Within SLE patients, after adjusting for age, race, sex, and waist circumference, EAT volume was associated with cumulative corticosteroid dose (P=0.007), current corticosteroid use (P<0.001), HDL cholesterol (P=0.033), and triglycerides (P=0.005). EAT was significantly correlated with CAC score (P<0.001), but the association was attenuated after adjustment for Framingham risk score (P=0.051).

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Conclusion—The increased EAT volume seen in SLE patients is associated with corticosteroid use. Corticosteroids could have adverse cardiovascular effects in SLE via an increase in EAT volume, a marker of risk in the general population.

Keywords

epicardial adipose tissue; systemic lupus erythematosus; atherosclerosis; coronary calcium score; corticosteroids

Introduction

Systemic lupus erythematosus (SLE), a disease primarily affecting young women, is characterized predominantly by inflammation and immune dysregulation (1). In the past two decades, mortality of SLE patients has declined; the five-year survival has increased to nearly ninety percent (2), perhaps secondary to earlier diagnosis and earlier treatment with immunomodulators (3). In spite of this, morbidity and mortality secondary to premature cardiovascular disease continues to be substantially increased (4,5). The pathogenesis of accelerated cardiovascular disease in this population has not been defined and is probably multifactorial. Factors that may influence early cardiovascular disease in lupus range from traditional cardiovascular risk factors (6) to increased concentrations of inflammatory cytokines and adipokines, disease activity and immunosuppressive medications such as corticosteroids.

Epicardial adipose tissue (EAT) has emerged as a potential contributor to atherosclerotic plaque formation, likely via a paracrine effect on the coronary arteries (7). In fact, recent literature suggests that EAT is associated with non-calcified, potentially vulnerable, plaque (8) and it correlates with ischemia on nuclear imaging (9,10). Furthermore, EAT was predictive of incident cardiovascular events independent of conventional risk factors and body mass index (BMI) in the Multi Ethnic Study of Atherosclerosis (MESA) (11) and another observational study (12).

The aim of this study was to measure EAT volume in patients with SLE and a matched group of asymptomatic subjects, and to assess the association of EAT with markers of cardiovascular risk as well as subclinical atherosclerosis, disease activity and damage and immunoactivation in SLE.

Methods

Study Cohort and Study Design

This was a cross-sectional study including 162 patients with SLE and 86 controls participating in ongoing studies of cardiovascular risk and described in detail in previous publications (13–15). We recruited more SLE patients than controls to better characterize factors that predispose to atherosclerosis in SLE. The two groups were frequency-matched for age, race and sex so that the distribution of these parameters remained similar in the two groups.

The study was approved by the Vanderbilt University Institutional Review Board and all subjects gave written informed consent. Consecutive eligible patients, age >18 years, who met the classification criteria for SLE (16) and had disease duration >1 year, were enrolled. Controls did not meet the classification criteria for SLE or any other autoimmune disease and were frequency-matched for age, sex and race so that the two groups did not differ materially with regard to these variables. Detailed descriptions of the recruitment procedures and study design have been reported previously (13–15). Patients and controls with a history

of angina, myocardial infarction, stroke, or chronic kidney disease receiving dialysis or awaiting renal transplant were excluded from this study.

Patients and controls were evaluated using a standardized clinical interview, physical examination, laboratory tests, and, in patients, review of the medical record. Clinical and laboratory characteristics collected included anthropomorphic measures, blood pressure measurement, lipid profile, inflammatory indices, and cytokine and adipokine levels as described previously (15). Additionally, information regarding Framingham risk factors, medication usage, disease activity (systemic lupus erythematosus disease activity index: SLEDAI) and damage accrual (systemic lupus international collaborative clinics: SLICC) was collected. For assessment of SLEDAI and SLICC we used previously validated methodologies (17,18).

Coronary Artery Calcium Score Measurement

An electron beam computed tomography C-150 scanner (GE Imatron, San Francisco, CA) was used to image patients 110 SLE patients and 78 controls; the remaining 52 SLE patients and 8 controls underwent coronary artery calcium imaging with a 64-slice multidetector CT (Light-Speed VCT, GE, Milwaukee, WI). A total of 40 slices of 3 mm thickness were obtained during a single breath-holding period of 20 seconds duration. Tomographic imaging was electrocardiographically triggered at 80 percent of the R-R interval. A calcified coronary plaque was considered present, if at least three contiguous pixels with a minimal attenuation of 130 Hounsfield units were measured. The acquired images were reviewed in a core imaging laboratory on a NetraMD workstation (ScImage, Los Altos, CA). The degree of coronary-artery calcification was calculated as described by Agatston et al (19). All scores were measured by an investigator blinded to the subjects' clinical status. The average radiation exposure was 1.2 ± 2 mSv per patient.

EAT Volume Measurement

EAT volume was measured on the same axial images used for coronary artery calcium analysis, using the Volume Analysis software tool of the Leonardo workstation (Leonardo, Siemens, Erlangen, Germany), as previously described (20). All slices from the bifurcation of the pulmonary artery to the diaphragm were used for the analyses. The region of interest containing the heart and the surrounding epicardial adipose tissue was assessed by manually tracing the epicardium in the axial slices; then a threshold of -190 to -30 HU units was applied to isolate the fat-containing voxels. The fat voxels were then summed to obtain the total EAT volume in cm^3 . All measurements were made by two investigators (AL and GH), blind to the subjects' clinical status.

Statistical Analysis

Descriptive statistics are presented as frequencies and percentage (%) for categorical variables and mean with standard deviation (mean \pm SD), or median with interquartile range (median [IQR]) according to the distribution of the continuous variables. Demographic and clinical factors were compared between SLE and controls using Wilcoxon rank sum test or a Pearson chi-square test, as appropriate.

The independent association between disease status (SLE or control) and EAT volume as the outcome variable was assessed using multivariable linear regression models with adjustment for age, race, and sex, and in separate model with additional adjustment for waist circumference (a measure of visceral adiposity). Among patients with SLE, we evaluated the relationship between EAT volume and anthropomorphic measures, demographics, disease activity, treatment, inflammation, cardiovascular risk factors, cytokines and adipokines. Wilcoxon's rank sum test or Spearman's rank correlation coefficients (ρ) were used to

assess the bivariate relationships between categorical and continuous variables and EAT. The independent associations were examined by multivariable linear regression with adjustment for age, race and sex as covariates, and additional adjustment for waist circumference.

The association of EAT volume with CAC score was examined with a proportional odds logistic regression model (21,22) where CAC was a dependent variable and EAT an independent variable adjusting for Framingham risk score. The proportional odds logistic model was used because CAC was heavily skewed and no mathematical transformation provided normality in its residuals. EAT volume was included as a non-linear factor in assessing its independent association with coronary calcification.

The association between corticosteroid use and EAT in patients with SLE was examined using multivariable linear regression where EAT was the dependent variable and corticosteroid the independent variable with adjustment for age, sex, race and waist circumference. The natural logarithm-transformation of EAT achieved normality of residuals, thus the assumption of linear regression was met. To illustrate the relationship between EAT volume and cumulative corticosteroid use, patients with SLE were categorized into four quartiles based on cumulative lifetime corticosteroid exposure that ranged from 0 to 172 g. Among SLE patients, multivariable linear regression modeling was applied to assess the independent association between inflammatory markers and EAT volume adjusting for age, sex, race and waist circumference. Concentrations of CRP, IL-6, TNF- α , triglycerides, homocysteine, and homeostatic model assessment (HOMA) were natural logarithm-transformed to improve normality. Waist circumference was included as a non-linear factor because a non-linear relationship with EAT was detected. Among women, the effect of menopausal status on the association between disease status and EAT volume was assessed using a multivariable linear regression model with interaction term of menopausal status and disease status and covariates for adjustment age, race, waist circumference.

Statistical analyses were performed using R version 2.10.0 (<http://www.r-project.org>). A two-sided significance level of 5% was required for consideration as statistical significant.

Results

Clinical characteristics of subjects

The clinical characteristics of SLE patients and controls are presented in Table 1. In SLE patients the median disease duration from onset of first symptom was 7 years (IQR: 3–12). Compared to controls, SLE patients had a larger waist circumference and waist-to-hip ratio, a higher prevalence of hypertension and a larger coronary artery calcium score. Furthermore, SLE patients had higher serum levels of homocysteine, and triglycerides and lower LDL cholesterol.

Association of disease status with EAT volume

SLE patients had a larger EAT volume ($96.8 \pm 45.9 \text{ cm}^3$) than controls ($78.2 \pm 40.7 \text{ cm}^3$, $P=0.001$; Figure 1). EAT volume was 31% (95% CI, 16.5% – 47.4%, $P<0.001$) larger in SLE patients than in controls, after adjustment for age, sex, and race. After additional adjustment for waist circumference, EAT volume was still significantly greater in SLE patients than controls (15.7% larger volume, 95% CI: 4.2%, 28.4%, $P=0.007$). Since hypertension has been associated with an increased EAT volume in a prior publication (23), we further adjusted the analyses for this risk factor and found that EAT volume remained significantly greater in SLE patients than controls (15.3% larger volume, 95% CI: 3.5%, 28.4%, $P=0.01$).

In analyses conducted among women only, EAT volume was significantly increased in both pre and post-menopausal women (data not shown).

Association of clinical variables with EAT volume in patients with SLE

In patients with SLE, EAT volume was positively correlated with 13 different variables (Table 2) and negatively correlated with adiponectin. After adjustment for age, race sex, and waist circumference, significant associations with EAT volume remained only for cumulative corticosteroid dose ($P=0.007$), current corticosteroid use ($P<0.001$), HDL cholesterol ($P=0.03$), and triglycerides ($P=0.005$).

Coronary calcium score was positively correlated with EAT volume (Table 2 $\rho=0.31$, $P<0.001$); after adjustment for Framingham risk score the association was attenuated (OR=1.63; 95% CI: 0.72–3.68, $P=0.051$ per each IQR [62.3, 124.6] cm^3 increment in EAT volume). However, after further adjustment for waist circumference the association was again significant ($P=0.04$).

Association of corticosteroid use with EAT volume

Increasing cumulative corticosteroid exposure was associated with increasing EAT in SLE patients after adjusting for age, sex, race and waist circumference ($P=0.007$). We also examined the association of EAT volume with quartiles of cumulative dose of corticosteroids using SLE subjects with cumulative corticosteroid dose between 0 and 2732 mg (1st quartile) as a reference group (Figure 2). SLE subjects with cumulative corticosteroid dose between 11,428 and 27,375 mg (3rd quartile) had a 32% (95% CI: 12% – 56%) larger EAT volume compared to SLE with corticosteroids dose in 1st quartile).

Among patients with SLE, there was no association between inflammatory markers (CRP, TNF- α , ESR) and EAT volume after adjusting for age, race, sex, waist circumference, and cumulative or current steroid use (all P values >0.1). There was a positive association between EAT volume and IL-6 after adjusting for age, race, sex, waist circumference and current corticosteroid use ($P=0.02$); however, the effect was attenuated after adjusting for cumulative rather than current corticosteroid use ($P=0.075$).

Discussion

Main results and technical considerations

This is the first report of EAT volume measurement in a cohort of SLE patients and a matched control group, and it expands previous findings in the same cohort of an increased coronary atherosclerotic burden, as assessed by coronary artery calcium (13–15). The main finding of the present study was that SLE patients have an increased burden of adipose tissue surrounding the coronary arteries.

Measurement of epicardial adipose volume on cardiac CT imaging is highly reproducible (24) and easily performed on the same images obtained for other purposes (in this case measurement of coronary artery calcium). While it employs radiation, the exposure is very low, and no iodine contrast administration is required (25). Obviously, EAT volume measurement is also feasible in contrast CT studies (8).

Atherosclerosis and contribution of corticosteroid therapy

SLE is associated with premature atherosclerosis; young women with SLE have almost double the risk of suffering an acute myocardial infarction compared to controls (5). The pathophysiological link between SLE and atherosclerosis is not fully understood; the cardiovascular risk of SLE patients is greater than what can be estimated from traditional

cardiovascular risk factors (6) and it is independently associated with the duration of disease (1). There is evidence supporting the role of inflammation and prothrombotic state in the development of atherosclerosis in patients with SLE (26).

The main finding of the present study, i.e. increased EAT volume in SLE patients compared to controls, provides a possible link between SLE and atherosclerosis. Furthermore, the association between increased corticosteroid exposure and greater EAT volume in SLE suggests a mechanism whereby corticosteroids may have deleterious cardiovascular effects. Indeed, corticosteroids are known to induce accumulation of visceral fat and in specific subcutaneous compartments (27). Of note, these phenotypic changes are associated with biochemical features typical of the metabolic syndrome (28), which could help explain some of the pro-atherosclerotic trends reported in these patients.

As we and others have shown, EAT is associated with atherosclerosis and its complications (8,9,11,12,20,29–31). Likely, EAT is not an innocent bystander, but it plays a pathogenetic role in the development of atherosclerosis, mediated through its metabolic effects both at a paracrine and a systemic level (7). EAT is a source of pro-inflammatory cytokines, including IL6, TNF- α , leptin, and MCP1. Due to its proximity to the coronary arteries, the inflammatory milieu it creates may fuel the atherosclerotic process (i.e. paracrine effect). Additionally, this type of adipose tissue secretes more inflammatory cytokines than subcutaneous fat and may therefore have a systemic inflammatory effect (32).

It is of interest that in our study population EAT volume was associated with coronary artery calcium, a marker of coronary atherosclerosis, after adjustment for Framingham risk score and waist circumference. This is in line with previous studies (31), and further supports the link between EAT and coronary atherosclerosis. Increased EAT volume has also been reported in patients with non-calcified coronary plaques, low-density plaques, and positive remodeling (8,33), features thought to represent plaque vulnerability (34).

Inflammatory markers and epicardial fat

Within our SLE patient group we investigated the association of disease-related factors and EAT volume and we found that inflammatory markers were not associated with EAT volume, except for a marginal association between EAT volume and IL-6; this finding supports earlier work from this cohort of SLE patients, where IL-6 was associated with increased inflammation, BMI, an adverse lipid profile and coronary artery calcium (13). However, we did not find an association between underlying disease activity or chronic lupus damage and EAT volume. This lack of association may be due to an intermediary role played by corticosteroid steroid use, since SLE patients with greater disease activity receive more corticosteroids, and corticosteroids may be on the causal pathway for EAT. Thus, the association of disease activity with increased EAT volume may not be reflected by adjustment for corticosteroid use.

Limitations

There were a few limitations in this study. The majority of patients and controls were Caucasian. Since this is a cross-sectional study, no cause-and-effect relationship can be established, and we have no hard outcomes. Some of the laboratory values shown in Table 2 were not available for all patients.

Conclusions

In conclusion, EAT is increased in SLE patients and it is marginally associated with the burden of coronary atherosclerosis as estimated by coronary artery calcium. The increase in EAT in SLE may be in part explained by use of corticosteroids and may contribute to the

poor cardiovascular outcomes in lupus. A longer follow up in larger cohorts of patients may offer insight into the association of EAT with hard events in SLE patients.

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- The epicardial adipose tissue volume on chest computed tomography was 31% larger (95% CI, 16.5% – 47.4%) in 162 SLE patients than 86 matched controls (P<0.001 adjusted for age, sex, and race; after additional adjustment for waist circumference P=0.007).
- In SLE patients, after adjusting for age, race, sex, and waist circumference, EAT volume was associated with cumulative corticosteroid dose (P=0.007), current corticosteroid use (P<0.001), HDL cholesterol (P=0.033), and triglycerides (P=0.005).

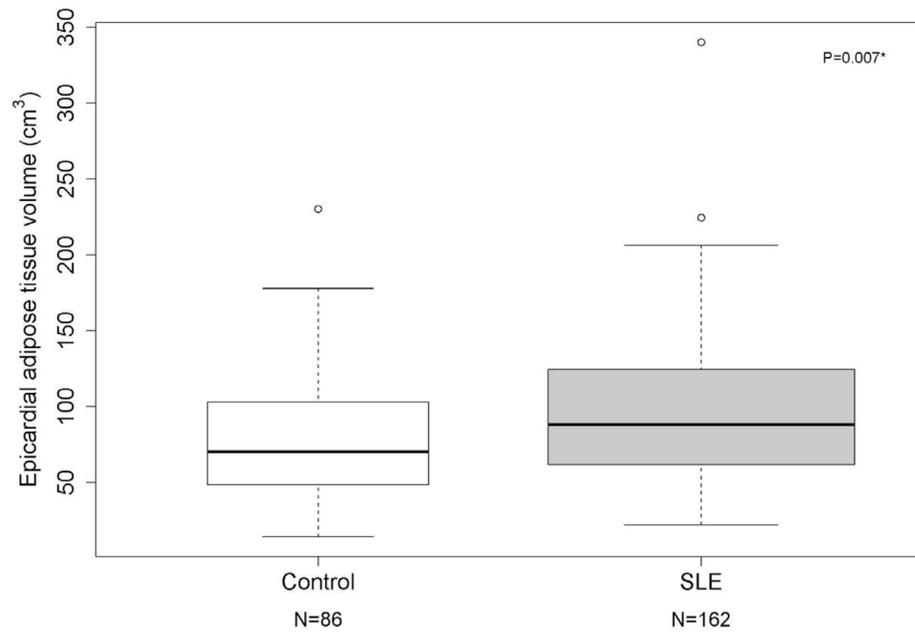


Figure 1.

Epicardial adipose tissue volume in SLE patients and control subjects.

Data are presented as box plots, where boxes represent the interquartile range (IQR), the horizontal lines within boxes represent the median, and the horizontal lines outside the boxes represent the lower quartile minus 1.5 times the IQR or the upper quartile plus 1.5 times the IQR.

* P value is from multivariable regression analysis assessing the independent association of disease status with epicardial adipose tissue volume with adjustment for age, sex, race and waist circumference.

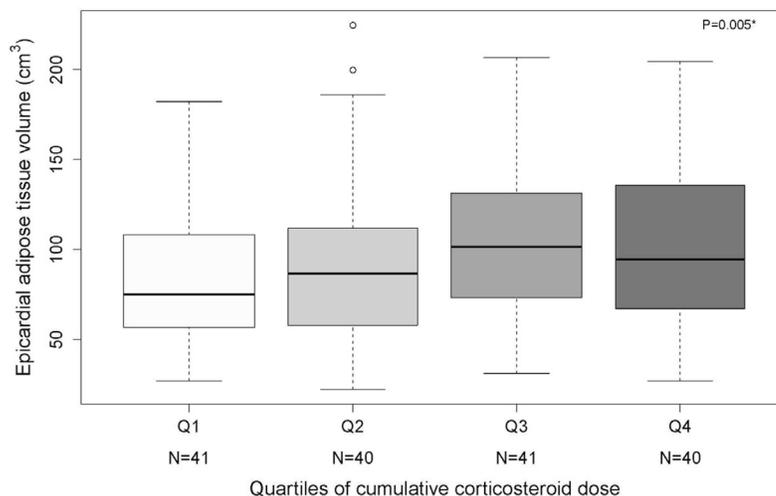


Figure 2.

Epicardial adipose tissue volume in SLE patients by cumulative corticosteroid dose. Data are presented as box plots, where boxes represent the interquartile range (IQR), the lines within boxes represent the median, and the lines outside the boxes represent the lower quartile minus 1.5 times the IQR or the upper quartile plus 1.5 times the IQR.

Q1: Cumulative corticosteroid dose between 0 and 2,732 mg

Q2: Cumulative corticosteroid dose between 2,732 and 11,428 mg

Q3: Cumulative corticosteroid dose between 11,428 and 27,375 mg

Q4: Cumulative corticosteroid dose \geq 27,375 mg

* The association between corticosteroid use and EAT in patients with SLE was examined using multivariable linear regression with adjustment for age, sex, race, waist circumference and cumulative corticosteroid dose as a continuous variable ($P=0.007$). For visual purposes, the figure illustrates exposure to quartiles of doses of corticosteroids; the model was also significant ($P=0.005$) when quartiles of cumulative corticosteroid doses were included as a categorical variable.

Table 1

Characteristics of study subjects

	Controls n = 86	SLE patients n = 162	P value
Age, years,	41.2±12.3	39.9±11.8	0.40
Sex, %Male	13%	9%	0.39
Waist circumference, cm	85.2±13.9	92.1±17.9	0.01
Waist/hip ratio	0.82±0.08	0.85±0.09	0.007
Body mass index, kg/m ² ,	26.8±5.2	29.0±7.5	0.06
Race, %Caucasian	74%	69%	0.33
Current Smokers, %	17%	22%	0.44
Hypertension, %	17%	40%	<0.001
Diabetes, %	1%	4%	0.25
HDL-cholesterol, mg/dl,	49.5±16.4	48.0±14.8	0.73
LDL-cholesterol, mg/dl,	109.6±32.6	102.1±37.2	0.02
Total cholesterol, mg/dl,	178.9±39.7	174.3±46.5	0.12
Triglycerides, mg/dl	100.1±57.4	120.9±62.4	0.002
Glucose, mg/dl	86.3±9.8	87.4±27.0	0.21
Homocysteine, μmol/l	8.1±2.1	9.7±3.3	<0.001
Creatinine, mg/dl	0.80±0.14	0.86±0.31	0.63
Systolic BP, mm Hg	118.0±14.0	118.0±16.0	0.71
Diastolic BP, mm Hg	70.9±10.0	72.6±12.4	0.45
Coronary calcium score	3.3±26.8	42.0±165.7	0.001
EAT volume, cm³	78.2±40.7	96.8±45.9	0.001

Continuous variables are presented as mean±SD. Categorical variables are presented as percentages.

BP= blood pressure; EAT= epicardial adipose tissue volume; HDL= high density lipoprotein; LDL= low density lipoprotein; SLE= systemic lupus erythematosus

Table 2
Association between clinical and laboratory measures and EAT volume in patients with SLE

	N	Spearman ρ	Unadjusted P value	Adjusted P* value	Adjusted P*** value
Anthropomorphic measures					
Waist circumference	155	0.65	<0.001	<0.001	
Body mass index	162	0.49	<0.001	<0.001	0.14
Waist/hip ratio	155	0.47	<0.001	<0.001	0.26
Disease or Treatment					
Cumulative steroid use	162	0.18	0.02	<0.01	0.007
Current steroid use	162	NA	0.06	0.01	<0.001
SLEDAI	162	0.03	0.73	0.17	0.76
SLICC	162	0.14	0.08	0.12	0.29
Inflammation					
hs-CRP	142	0.21	0.01	0.03	0.60
IL-6	108	-0.08	0.39	0.44	0.06
TNF- α	108	-0.01	0.93	0.46	0.76
ESR	160	-0.06	0.44	0.26	0.37
Cardiovascular risk markers					
Total cholesterol	150	0.27	0.001	0.003	0.10
HDL cholesterol	150	-0.02	0.80	0.93	0.03
LDL cholesterol	150	0.20	0.01	0.03	0.66
Triglycerides	150	0.37	<0.001	<0.001	0.005
Hypertension	162	NA	0.02	0.04	0.85
Current smoking	162	NA	0.86	0.21	0.16
HOMA	106	0.36	<0.001	<0.001	0.93
Homocysteine	156	0.25	0.002	0.04	0.31
Adipokines					
Leptin	108	0.42	<0.001	<0.001	0.15
Adiponectin	108	-0.27	0.004	0.03	0.73
Coronary atherosclerosis					

	N	Spearman ρ	Unadjusted P value	Adjusted P* value	Adjusted P** value
Calcium score	162	0.31	<0.001	0.051***	0.04 [†]

HOMA: homeostatic model assessment

NA: Not applicable (for categorical variables a Chi-squared test was performed).

SLEDAI: systemic lupus erythematosus disease activity index (disease activity index)

SLICC: systemic lupus international collaborative clinics (disease damage index)

* Multivariable linear regression was used for adjustment of age, race and sex.

** Multivariable linear regression was used for adjustment of age, race, sex and waist circumference.

*** Proportional odds model with adjustment for Framingham risk score.

[†] Proportional odds model with adjustment for Framingham risk score and waist circumference