Inflammatory Mechanisms Affecting the Lipid Profile in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Increased low density lipoprotein (LDL) cholesterol and triglycerides, and decreased high density lipoprotein (HDL) cholesterol concentrations are associated with adverse cardiovascular risk in the general population. Patients with systemic lupus erythematosus (SLE) have an altered lipid profile characterized by increased triglycerides and decreased HDL cholesterol concentrations. We examined the relationships between lipid concentrations, cytokines, and inflammatory markers in patients with SLE.

Methods. Fasting lipid concentrations, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured in 110 patients with SLE. Disease activity was quantified by the SLE Disease Activity Index (SLEDAI), and disease damage by the Systemic Lupus International Collaborating Clinics (SLICC) score. Concentrations of circulating tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and insulin were measured and insulin sensitivity calculated.

Results. Lower concentrations of HDL cholesterol were independently associated with higher ESR ($p < 0.001$), IL-6 ($p = 0.02$), SLEDAI ($p = 0.04$), and TNF-α ($p = 0.04$) after adjustment for age, sex, race, body mass index, insulin sensitivity, and current use of corticosteroids or hydroxychloroquine. Triglyceride concentrations were associated with higher CRP concentrations ($p = 0.02$) and SLICC score ($p = 0.04$).

Conclusion. Deleterious changes in lipid profile are independently associated with higher concentrations of markers and mediators of inflammation and disease activity and damage in patients with SLE. (First Release July 15 2007; J Rheumatol 2007;34:1849–54)

Key Indexing Terms:
CHOLESTEROL TRIGLYCERIDES CYTOKINES
SYSTEMIC LUPUS ERYTHEMATOSUS INFLAMMATION

Systemic lupus erythematosus (SLE) is an inflammatory disease leading to accelerated atherosclerosis[1,2]. Epidemiological data indicate that young women with SLE have a cardiovascular risk several times higher than that of an age-matched control population[3]. Concordantly, patients with SLE have an increased prevalence of atherosclerosis and increased risk of hospitalization due to myocardial infarction[4,5].

In the general population high concentrations of total and low density lipoprotein (LDL) cholesterol, and low concentrations of high density lipoprotein (HDL) cholesterol are major independent cardiovascular risk factors[6]; high concentrations of triglycerides are also associated with increased risk of cardiovascular disease[6], particularly in women[7]. In patients with SLE, lipid profiles are altered; concentrations of HDL cholesterol are lower[8,9], and triglycerides higher, than those of control subjects[8-10]. Further, oxidative modification of LDL cholesterol including $ß_2$-glycoprotein I ox-LDL complexes are associated with arterial thrombosis[11]. In addition to the deleterious effect on the cardiovascular system, dyslipidemia may also contribute to noncardiovascular risk in patients with lupus. For example, higher cholesterol concentrations are associated with increased mortality and a greater risk of adverse renal outcomes in patients with SLE[12]. Therefore, a better understanding of the mechanisms that lead to a decrease in HDL and an increase in triglyceride and LDL cholesterol concentrations in patients with SLE is of interest.

Diet and heredity are known to be major determinants of lipid concentrations, but the role of inflammation is less well recognized. In animal models, concentrations of tumor necrosis factor-α (TNF-α) are associated with increased serum cholesterol and decreased HDL cholesterol concentrations[13], and in humans, inflammation during infection is associated with increased triglyceride concentrations[14]. Further, in patients

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Supported by grants HL04012, HL65082, and GM5M01-RR00095 from the National Institutes of Health and by a grant from the Lupus Foundation of America, Nashville Chapter. Dr. Avalos is supported in part by a grant from the American College of Rheumatology.

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Accepted for publication April 25, 2007.

with human immunodeficiency virus infection, inflammatory mediators such as interferon and TNF-α are associated with an increase in triglyceride and a decrease in HDL concentrations[15]. SLE induces cytokine activation. Some cytokines, including TNF-α and IL-6, may be not only biomarkers of disease activity[16], but also a link between inflammation and dyslipidemia. Recent data suggest that TNF-α is associated with lower HDL cholesterol and higher triglyceride concentrations in patients with SLE[17]. However, TNF-α also promotes insulin resistance[18], and insulin sensitivity is decreased in patients with SLE[19] and is related to cholesterol concentrations[20]. Further, medications such as corticosteroids and hydroxychloroquine[8,21] may affect lipid concentrations. There is little information available about the relationship between inflammation and the lipid profile of patients with SLE, independent of other factors such as medications and insulin sensitivity.

Previous work in this cohort of patients suggested there might be a relationship between alterations in lipid concentration and inflammation in patients with lupus[22]. Our study builds on this observation and specifically addresses the hypothesis raised: it examines the relationship between HDL, LDL, and triglyceride concentrations and other clinical variables and takes into account potential confounders such as body mass index (BMI), comedications, and insulin sensitivity that could have accounted for the initial correlations observed. Thus, we set out to examine the relationship between triglycerides, HDL and LDL cholesterol, and markers of inflammation, independent of the effect of traditional cardiovascular risk factors, insulin sensitivity, and medications.

MATERIALS AND METHODS

Outpatients older than 18 years of age, who met the classification criteria of SLE[23] and had disease duration longer than one year, were enrolled as part of an ongoing project to evaluate atherosclerosis in patients with SLE[1,19,22,24-26]. Patients were recruited from the practices of local rheumatologists in Nashville, through the Lupus Foundation, and by local advertisements. For our study, we excluded patients who were currently taking lipid-lowering drugs.

Medical records were reviewed to confirm classification criteria of SLE and to obtain the results of anti dsDNA, anticardiolipin antibodies, and lupus anticoagulant. A positive antiphospholipid antibody test was defined as the presence of either a positive test for anticardiolipin antibodies (IgG and/or IgM) or lupus anticoagulant[27].

Patient assessment included a clinical interview, examination, and laboratory tests. Family history of coronary disease was defined as a first-degree relative who had had a myocardial infarction or stroke before the age of 55 years in men or 65 in women[28]. Height and weight were measured and BMI calculated by dividing the weight (kg) by the square of the height (m). Blood pressure was recorded as the mean of 2 measurements obtained 5 min apart after resting for at least 10 min. Fasting glucose, total cholesterol, HDL, LDL, triglycerides, Lp(a) lipoprotein, homocysteine, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured by standard techniques and fasting insulin concentrations using ELISA (Lincoplex). A homeostasis model assessment (HOMA) index was calculated with the following formula: [fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5][29]. Disease activity and damage were scored with the SLE Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinics damage index (SLICC), respectively[30,31].

The study was approved by the Institutional Review Committee at Vanderbilt University and all subjects gave written informed consent.

Laboratory tests. Blood was drawn from participants after an overnight fasting period and glucose, total cholesterol, HDL, triglycerides, Lp (a) lipoprotein, and homocysteine concentrations were measured, and LDL concentrations calculated. Plasma samples, stored at –70°C, were analyzed by ELISA (Linco Research) to measure concentrations of TNF-α, IL-6, and insulin. A HOMA index was calculated as a measure of insulin sensitivity.

Statistical methods. Demographic characteristics are presented for continuous variables as means and standard deviations or medians and interquartile ranges (IQR) based on their distribution and as frequencies and percentages for categorical variables. The analyses were performed in 2 phases. First, Spearman's correlation coefficients were calculated to examine the bivariate association between HDL and LDL cholesterol, and triglycerides with disease activity and damage, markers of inflammation, insulin sensitivity, cytokine concentrations, and medication use. In addition, lipid concentrations were compared in patients with and without antiphospholipid antibodies. Second, multiple linear regressions models were applied to assess whether these associations were independent of age, sex, race, BMI, insulin sensitivity, and use of corticosteroids and antimalarials. These covariates were chosen *a priori* for adjustment based on their clinical relevance. Residuals of the multiple linear regressions were assessed to ensure model assumptions. We performed box-Cox transformation of the outcome variables to obtain normality of the regression residuals to ensure model assumption. For continuous independent variables nonlinear effect was assessed by using restricted cubic splines[32]. All analyses used a 2-sided level of significance of 5% and were performed with R 2.1.0 (www.r-project.org).

RESULTS

Patient characteristics. Patients with lupus were 40 ± 12 years old, 90.9% women, and 69.1% Caucasian. Sixty percent were taking corticosteroids and 62.7% antimalarials (Table 1). Their median (IQR) disease duration was 7 (3–12) years, and the median SLEDAI score was 4 (1–6) and current corticosteroid dose 5 (0–7) mg of prednisone or equivalent per day. The mean concentration of HDL cholesterol was 47.6 ± 14.7 mg/dl, LDL cholesterol 102.8 ± 37.9 mg/dl, and triglycerides 121.2 ± 60.2 mg/dl (Table 1).

Relationship between inflammation, disease, insulin sensitivity, and lipids. Lower concentrations of HDL cholesterol correlated with ESR (rho = –0.44), TNF-α (rho = –0.38), IL-6 (rho = –0.31), and the SLEDAI score (rho = –0.21). Higher concentrations of LDL cholesterol correlated with lower concentrations of TNF-α (rho = –0.22). Triglycerides were associated with higher levels of CRP (rho = 0.36), TNF-α (rho = 0.26), IL-6 (rho = 0.23), ESR (rho = 0.20), and the SLICC score (rho = 0.22). Correlation coefficients are shown in Figure 1. A higher HOMA index, representing decreased insulin sensitivity, was associated with lower HDL (rho = –0.33) and higher triglyceride concentrations (rho = 0.23). Cumulative corticosteroid dose was associated with higher triglyceride concentrations (rho = 0.29, $p = 0.002$), but neither cumulative exposure to hydroxychloroquine nor current hydroxychloroquine use was associated with lipid concentrations.

The associations between HDL cholesterol and ESR ($p < 0.001$), IL-6 ($p = 0.02$), SLEDAI score ($p = 0.04$), and TNF-α ($p = 0.04$) remained statistically significant after adjustment

Table 1. Characteristics of patients with systemic lupus erythematosus (SLE).

General Characteristics	Patients (n = 110)
Age (yrs)	40.4 ± 11.6
Female (%)	90.9
Caucasian (%)	69.1
SLE characteristics (%)	
Positive anti-dsDNA*	38.4
Creatinine > 1.2 mg/dl	5.5
Positive antiphospholipid antibody*	29.7
Current use of corticosteroids	60
Current use of antimalarials	63
Traditional cardiovascular risk factors	
Systolic blood pressure (mm Hg)	120.8 ± 18.2
Diastolic blood pressure (mm Hg)	74.2 ± 13.9
Body mass index (BMI) (kg/m^2)	29.1 ± 7.4
Obesity (BMI > 30 kg/m^2) (%)	41
Current smokers (%)	26
Cumulative smoking (pack-yrs)	5.6 ± 11.2
Diabetes (%)	3.6
Family history of coronary disease (%)	20
Lipid profile and other laboratory tests	
Total cholesterol (mg/dl)	174.6 ± 45.2
High density lipoprotein (HDL) (mg/dl)	47.6 ± 14.7
Low density lipoprotein (LDL) (mg/dl)	102.8 ± 37.9
Triglycerides (mg/dl)	121.2 ± 60.2
Lipoprotein(a) (mg/dl)	22.4 ± 26.0
Glucose (mg/dl)	87.2 ± 25.9
Homocysteine (µmol/l)	9.5 ± 3.1
HOMA index	1.9 ± 1.7
Total cholesterol > 240 mg/dl (%)	6.4
LDL cholesterol > 129 mg/dl (%)	24.6
HDL cholesterol < 32 mg/dl (%)	14.6
Triglycerides > 290 mg/dl (%)	0.9
Homocysteine > 15 µmol/l (%)	5.5
HOMA > 2.114 units* (%)	40.9

* Results were available for 98 (anti-dsDNA) and 101 patients (antiphospholipid antibodies). HOMA: homeostasis model assessment.

for age, sex, race, BMI, HOMA, and current use of corticosteroids or hydroxychloroquine. Similarly, the relationship between triglyceride concentrations and SLICC (p = 0.04) and CRP (p = 0.02) remained statistically significant after adjustment for age, sex, race, BMI, HOMA, and current use of corticosteroids or hydroxychloroquine (Figure 2).

Patients with a positive anti-dsDNA antibody test had significantly lower concentrations of HDL cholesterol (44 ± 14 mg/dl) than those with a negative test (50 ± 14 mg/dl), p = 0.03. Concentrations of LDL cholesterol (p = 0.14) and triglycerides (p = 0.08) were not significantly different in these 2 groups of patients. Patients with an antiphospholipid antibody had lower concentrations of total cholesterol (160 ± 34 mg/dl) compared to patients without these antibodies (181 ± 48 mg/dl) (p = 0.05). HDL (p = 0.12) and LDL (p = 0.08) cholesterol concentrations did not differ significantly in patients with positive and negative tests for antiphospholipid antibodies.

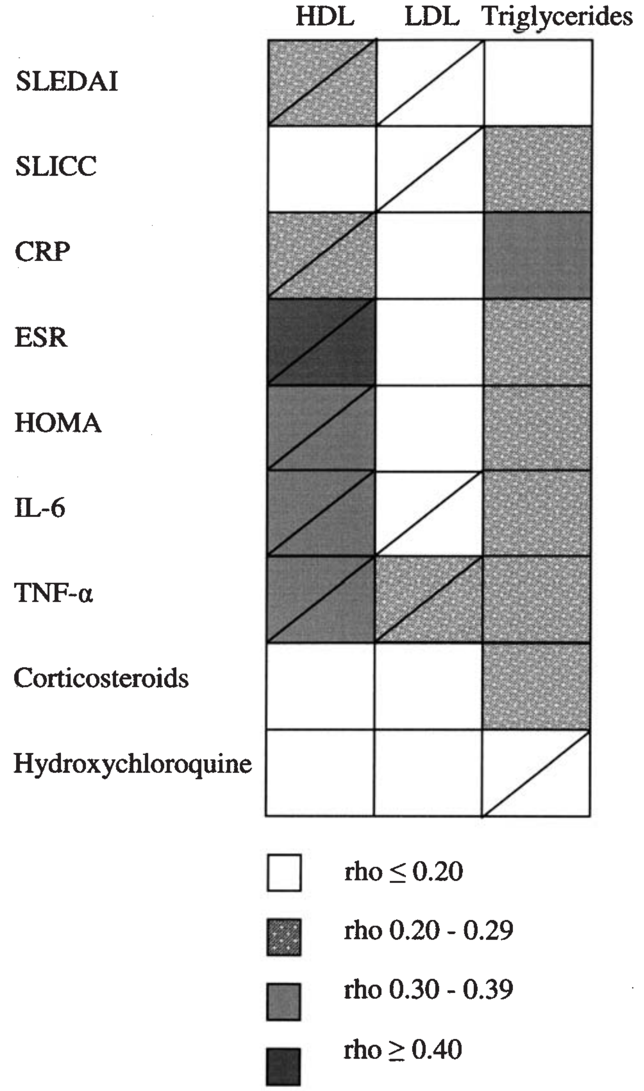

Figure 1. Spearman correlation coefficients show associations among disease activity, damage, markers of inflammation, cytokines, and treatment with cholesterol and triglyceride concentrations. Diagonal lines represent negative correlations. SLEDAI: SLE Disease Activity Index; SLICC: SLE International Collaborating Clinics Damage Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HOMA: homeostasis model assessment of insulin resistance; IL-6: interleukin 6; TNF-α: tumor necrosis factor-α.

DISCUSSION

The major novel finding of our study is the independent association between concentrations of LDL cholesterol, triglycerides, and HDL cholesterol and cytokines, other inflammatory markers, disease activity, and damage in patients with lupus.

In patients with SLE, earlier studies suggested an association between disease activity and increased triglyceride concentrations[9], and Svenungsson, *et al*, concordant with our findings, reported that higher triglycerides and lower HDL cholesterol concentrations correlated with TNF concentrations and disease activity, independent of the use of medica-

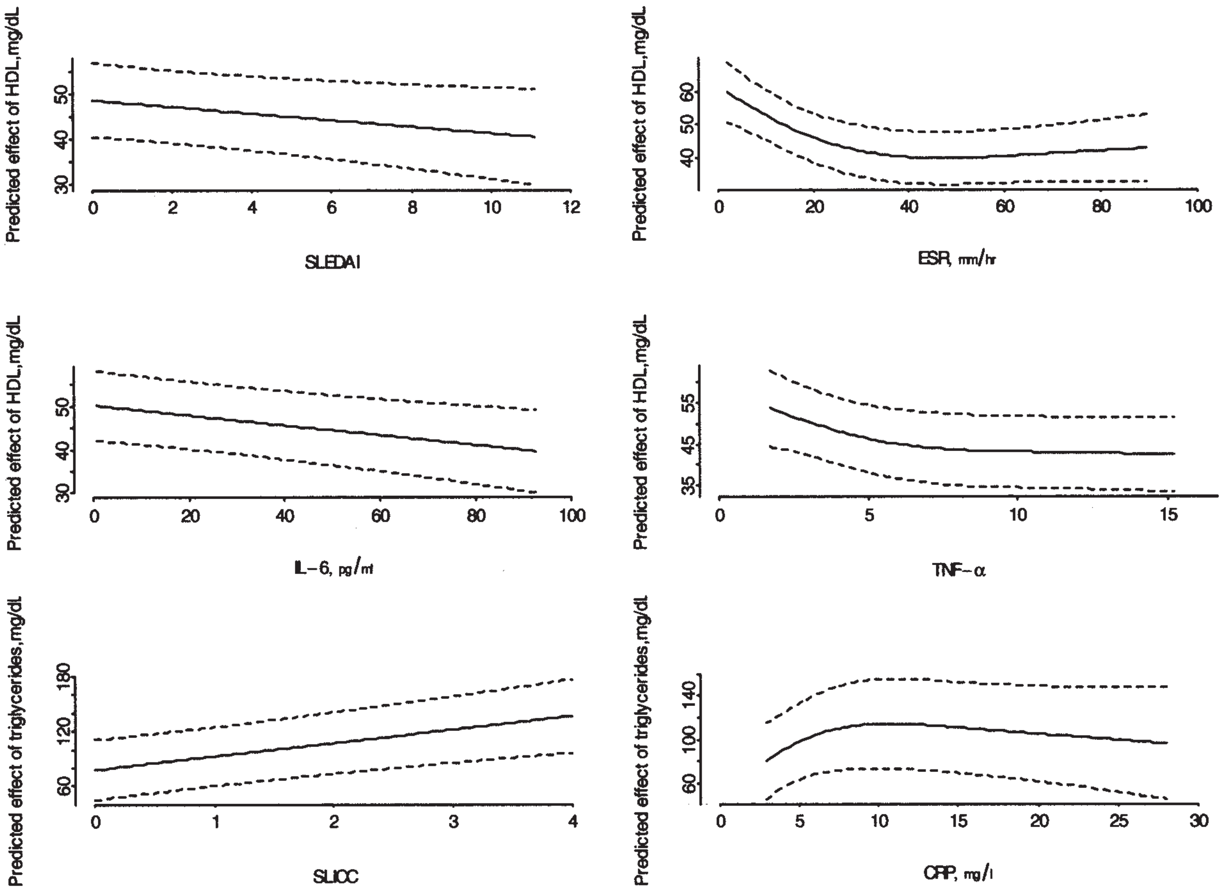

Figure 2. Factors independently associated with triglycerides and HDL cholesterol. Results from the multivariate model after adjustment for age, sex, race, BMI, insulin sensitivity, and use of corticosteroids and antimalarials. Lines represent the association between triglycerides and HDL cholesterol with all the independent variables that were statistically significant after all adjustments. Broken lines represent 95% confidence intervals. SLEDAI: SLE Disease Activity Index; SLICC: SLE International Collaborating Clinics Damage Index.

tions (antimalarials and prednisolone) and proteinuria[17]. These effects can be mediated by different mechanisms; inflammatory cytokines may reduce production or activity of apoA-1, lecithin-cholesterol acyl transferase, cholesterol ester transfer protein, and lipoprotein lipase[33]. Reversal of inflammation may affect the lipid profile, and some studies report a beneficial effect of anti-TNF-α therapy in patients with rheumatoid arthritis (RA), another chronic inflammatory disease. For example, treatment with adalimumab, a humanized anti-TNF-α agent, increased HDL cholesterol within 2 weeks, and infliximab — a chimeric anti-TNF-α antibody — has been shown to decrease concentrations of HDL cholesterol[34,35]. However, other studies found no effect, or even deleterious effects on the lipid profile after treatment with infliximab over a 2-year period in patients with RA[36,37]. Our results show a negative correlation between TNF-α and HDL cholesterol and further identify additional inflammatory mediators, such as IL-6, that may link an altered lipid profile and inflammation in SLE.

Additional mechanisms explaining dyslipidemia in patients with SLE include altered metabolism of chylomicrons[38], the presence of autoantibodies to lipoprotein lipase[39,40], and the role of proinflammatory cytokines. Antibodies to lipoprotein lipase, which are associated with elevated markers of inflammation[40], have been linked to increased triglyceride concentrations[39,40]. Also, patients with SLE have altered chylomicron metabolism with decreased lipolysis and chylomicron remnant removal from the plasma[38]. In addition, as discussed in a recent review, inflammatory cytokines such as IL-6 and TNF-α may downregulate lipoprotein lipase activity, emphasizing the role of inflammation as a mechanism underlying hypertriglyceridemia[41].

IL-6 concentrations are inversely associated with HDL concentrations in the general population. Individuals with IL-6 concentrations in the highest tertile had more than twice the risk of having low HDL concentrations than those in the lowest tertile[42]; potential mechanisms for this include stimulation of phospholipase A[33], or modification of HDL with a subsequent increase in its clearance[42]. Because IL-6 is increased in patients with SLE and has been implicated in the mechanisms underlying tissue damage[43,44], its relationship with lipid concentrations is of interest.

Corticosteroids, antimalarials, and insulin sensitivity have been proposed as modifiers of the lipid profile in patients with SLE. In a longitudinal study of 264 patients with lupus, hydroxychloroquine in doses of 200 and 400 mg per day was independently associated with lower total cholesterol concentrations[21], and its role appeared to be enhanced in patients taking corticosteroids[45]. Also, increased concentrations of total cholesterol and triglycerides were associated with corticosteroid use[46]. Thus, it was important to undertake analyses adjusting for these factors.

Our data suggest that cumulative exposure to corticosteroids was associated with higher triglyceride concentrations, but exposure to hydroxychloroquine was not associated with lipid concentrations. In addition to the role of medications, insulin resistance is associated with increased triglyceride and LDL, and decreased HDL cholesterol concentrations[20]. We have recently reported that insulin sensitivity is decreased in patients with SLE[19]; corticosteroids, hydroxychloroquine, and inflammation can all alter insulin sensitivity[8,47-49] and could thus affect lipid concentrations by this mechanism. We found that insulin resistance, as measured by the HOMA index, was associated with lower concentrations of HDL cholesterol and higher concentrations of triglycerides.

Since some inflammatory markers are associated with a deleterious lipid profile in SLE, it may be possible to target both disease activity and dyslipidemia simultaneously. Data from the general population support this notion. For example, a randomized study indicated that atorvastatin decreased not only LDL cholesterol, but also several inflammatory cytokines, including TNF-α and IL-6[50]. Data in patients with RA are also informative. A recent report suggests that the atherogenic lipid profile observed in patients with early disease reverses after the disease is treated with methotrexate and prednisone[51].

Some limitations of our study should be considered. The patient population had relatively mild disease, and the results cannot be generalized to patients with more severe disease. However, the association between alterations in lipid profile and markers of inflammation may be even stronger in patients with more severe inflammation. We did not measure lipid subfractions or the antiinflammatory function of HDL. Recent data indicate that particular lipid subfractions play an important role in the initiation and progression of atherosclerosis[52], and that measurement of these subfractions may improve the prediction of coronary risk disease beyond the traditional lipid profile. In particular, increases in small LDL particles correlate with coronary artery calcification, and are related to incident coronary heart disease in women[53]. Moreover, it has recently been reported that patients with RA or SLE have proinflammatory HDL even when plasma concentrations of HDL cholesterol are normal[54].

We report a link between inflammation and an altered lipid profile, independent of age, sex, race, BMI, current treatment with corticosteroids or hydroxychloroquine, and insulin sensitivity, in patients with SLE. Further research is needed to examine the role of lipoprotein subparticles and to test the hypothesis that better control of inflammation may regulate lipid profile alterations in these patients.

ACKNOWLEDGMENT

We thank Carol Brannon for helping with patient recruitment.

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