

Changes in Lipid Profile Between Flare and Remission of Patients with Systemic Lupus Erythematosus: A Prospective Study

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ABSTRACT. Objective. To determine the lipid profile of patients with systemic lupus erythematosus (SLE) according to the disease activity, and to calculate the percentage of patients that diverged from optimal values.

Methods. Serum was collected from 52 patients with SLE at flare and at remission. SLE disease activity was measured by using the SLE Disease Activity Index (SLEDAI). Clinical and biological measures were evaluated in both situations. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride (TG) levels were analyzed after overnight fasting. We also calculated the atherogenic ratios of TC/HDL and LDL/HDL.

Results. SLE patients had significantly higher median TC/HDL and LDL/HDL ratios at flare than during remission: 4.5 ± 1.5 versus 3.9 ± 1.0 ($p = 0.007$) and 2.7 ± 1.1 versus 2.4 ± 0.8 ($p = 0.015$), respectively. The differences persisted after adjustments based on kidney disease and treatment but not after adjusting by creatinine clearance < 60 ml/min/1.73 m² in remission. The variation between flare and remission of the percentage of SLE patients with high-risk levels of lipid profile to desirable values, and vice versa, was statistically significant for the LDL/HDL ratio (9 vs 1; $p = 0.021$).

Conclusion. Our results reflect a higher risk of atherosclerosis phenomena in SLE patients during flare than during clinical remission. This might explain the propensity to develop coronary heart disease in patients with SLE. (J Rheumatol First Release June 15 2009; doi:10.3899/jrheum.081097)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
BIOLOGICAL MARKERS

DISEASE ACTIVITY

ARTERIOSCLEROSIS
CHOLESTEROL

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology. Premature coronary heart disease (CHD) has emerged as a major cause of morbidity and mortality in patients with SLE^{1,2}. Young women with SLE have an estimated 50-fold increased risk of myocardial infarction compared with age and sex-matched controls¹. The major cause of CHD in these patients is premature atherosclerosis disease³.

A small number of studies have attempted to identify the risk factors for CHD in SLE by comparing patients who have SLE and documented CHD with SLE patients who do not develop CHD^{1,4,5}. Elevated concentrations of total cholesterol (TC) were consistently identified by all the studies as a risk factor, and it may be responsible for the atherosclerosis process in these patients.

The dyslipoproteinemia observed in patients with SLE has a multifactor origin. It is complex to elucidate which factors are clearly involved in the pathophysiology of this lipid disorder. Among these factors, drugs (particularly steroids at high dose⁶⁻⁸), renal involvement⁷, and disease activity⁹ seem to have a leading role.

To our knowledge, no study in the literature in adult lupus has focused on the lipid profile in the same patient during flare and in remission to evaluate the effect of the disease activity. Sarkissian, *et al*^{10,11} published 2 reports of a retrospective study in pediatric lupus describing lipid profiles of an inception cohort, and evaluating the factors that could modify it using complex statistical analysis.

We believe this is the first prospective study assessing the variations in the lipid profile between flare and remission in

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Dr. Urquizu-Padilla was supported by funds provided by the Spanish Ministerio de Sanidad y Consumo via the Instituto de Salud Carlos III (CM04/00034).

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Accepted for publication March 9, 2009.

a cohort of patients with SLE; we also addressed the relationship with variables linked to SLE.

MATERIALS AND METHODS

Data were collected from 52 consecutive individuals with SLE who had had a flare of SLE and who later had a remission. All patients fulfilled at least 4 American College of Rheumatology revised criteria for the classification of SLE¹². SLE activity was assessed by the SLE Disease Activity Index (SLEDAI)¹³.

A flare was defined as any clinical event directly attributable to disease activity that required a change in treatment and that showed a SLEDAI result ≥ 6 . At the time of flare, a blood sample was taken and sent to the laboratory.

All patients who gave a blood sample during flare were followed periodically in order to detect remission. When clinical remission was detected, another blood sample was taken and analyzed. We considered the patient was in remission if the SLEDAI was ≤ 6 and when this result meant a 50% decrease from the SLEDAI flare score.

The patient's history was reviewed: demographic and SLE-related data were collected [disease status, atherosclerotic risk factors (Paffenbarger Physical Activity Questionnaire¹⁴ was used to measure the expenditure of kcal/week; we estimated the 10-year global risk of CHD with the Regicor¹⁵ and Dorica¹⁶ scales, which are adaptations of the Framingham scale according to the prevalence of independent risk factors and incidence of coronary events in Catalan and Spanish populations, respectively), laboratory findings, type of clinical symptoms at flare and during remission, and the treatment at the time of blood sampling and to treat the flare].

Subjects' written consent was obtained according to the Declaration of Helsinki, and the study design conformed to standards currently applied in Spain¹⁷.

Sample collection. Samples were extracted after overnight fasting. Whole blood was collected into plain tubes. Lipid analyses were all carried out on unfrozen samples. Total serum cholesterol (TC) and total triglycerides (TG) were tested by an automated colorimetric enzymatic method (Tokio 192-8512, Tokyo, Japan) on an Olympus AU-5400 analyzer (Olympus, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL) was determined by an automated colorimetric enzymatic method with antibodies against apolipoprotein B (apo B; Tokio 192-8512) on an Olympus AU-5400 analyzer. Low-density lipoprotein cholesterol (LDL) was calculated following Friedewald's equation [$LDL = TC - HDL - (TG/5)$] when the serum TG level was < 2.82 mmol/l. When TG values were > 2.82 mmol/l, LDL was determined by sequential ultracentrifugation¹⁸. The serum was adjusted to a density of 1.006 g/ml with sodium bromide solution and ultracentrifuged at 40,000 rpm for 21 h at 15°C in a Beckman L8-M rotor-type TFT 45.6. After centrifugation, the very-low-density lipoprotein cholesterol (VLDL) was carefully removed and LDL concentration was calculated as: $LDL = TC - HDL - VLDL$. In addition, LDL was corrected by subtracting the cholesterol portion of lipoprotein(a), estimated as $0.3 \times$ lipoprotein(a) concentration¹⁹.

Lipid profile levels of risk for coronary heart disease. The lipoprotein level of risk was determined based on the updated recommendations of the National Cholesterol Education Program (NCEP)²⁰. The NCEP guidelines suggest a desirable total cholesterol level < 5.17 mmol/l and define low HDL when < 1.03 mmol/l. Desirable levels of LDL and TG were defined as < 3.36 mmol/l and < 1.64 mmol/l, respectively. For the atherogenic ratios, we applied those proposed by the investigators of the Framingham study²¹: TC/HDL ratio ≤ 5 in men and ≤ 4.5 in women; and LDL/HDL ratio ≤ 3.5 in men and ≤ 3 in women.

Statistical analysis. Continuous variables were expressed as means \pm standard deviation (SD) or medians [interquartile range (IQR)] if data were skewed; categorical variables were expressed as numbers and percentages.

To evaluate differences in the categorical variables between the 2 disease stages (flare and remission) we used the McNemar test. To evaluate

continuous variables in the 2 disease stages we used the paired-sample T test for variables that followed a normal distribution and the Wilcoxon matched-pairs signed-rank test for variables that did not.

Since some drugs (especially high doses of prednisone) and kidney disease seem to alter the lipid profile, we constructed a general linear model for repeated measures to evaluate the changes between flare and remission for those significant variables, entering each of the following variables, as between-subjects factor (if categorical)/covariate (if continuous): renal flare, clearance of creatinine during remission < 60 ml/min/1.73 m², prednisone dose in flare > 10 mg/day, accumulated dose of prednisone (mg) until flare, treatment with antimalarials (at flare and at remission), and cyclosporine/tacrolimus and mycophenolate/azathioprine therapy during remission.

Mann-Whitney U test (for non-normal variables) or the independent samples t test (normal variables) for equality of means (along with Levene's test for equality of variances) was used to compare means between nonpaired groups. Relationships between 2 continuous variables were examined by Pearson's correlation coefficient (r) if both variables had normal distribution; otherwise, Spearman's rank correlation coefficient (r_s) was used.

p values (2-tailed) < 0.05 were considered statistically significant. All analyses were performed with the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 12.0.

RESULTS

Our patients were mainly female (n = 46; 88.5%) and Caucasian (45; 86.5%); other ethnic groups included 5 Latin American, 1 Gypsy, and 1 Arab. The median age was 31.1 ± 12.4 years. There were 9 (17.3%) obese patients (body mass index ≥ 30) and 13 patients (25%) had a sedentary lifestyle (< 2000 kcal/week). Other variables related to atherosclerosis, disease status, type of clinical symptomatology, and treatment are detailed in Table 1. No patient was diabetic and no patient had a history of either CHD or ictus.

Influence of disease activity on lipid profile. SLE patients had significantly higher mean levels of both atherogenic ratios during flare than during remission: TC/HDL ratio 4.5 ± 1.5 versus 3.9 ± 1.0 (p = 0.007) and LDL/HDL ratio 2.7 ± 1.1 versus 2.4 ± 0.8 (p = 0.015). We found no significant differences between values during flare and during remission for TC, HDL, LDL, and TG (Table 2). Nevertheless, a tendency to a worse lipid profile was observed at flare. After excluding menopausal women from the analysis, we observed the same result: TC/HDL ratio 4.6 ± 1.5 versus 4.0 ± 1.1 (p = 0.005) and LDL/HDL ratio (2.7 ± 1.1 versus 2.4 ± 0.8 (p = 0.015), without finding significant differences between values during flare and during remission for the other lipid profile variables.

When we applied a general linear model for repeated measures, we found that the changes between flare and remission in the TC/HDL and LDL/HDL ratios retained statistical significance after adjusting for the effect of renal flare (p = 0.009 and p = 0.003, respectively), prednisone dose during flare > 10 mg/day (p = 0.005 and p = 0.024), accumulated dose of prednisone until flare (p = 0.046 and p = 0.023), use of antimalarial drugs during flare (p = 0.007 and p = 0.017) or remission (p = 0.007 and p = 0.023), cyclosporine/tacrolimus treatment during remission

Table 1. Disease status variables, immunological and serological features, atherosclerosis-related variables, clinical symptomatology, and treatment received during flare and remission.

Features	Flare	Remission	p
Disease status			
Duration from diagnosis, yrs, mean ± SD	5.8 ± 5.4		
Duration since flare, mo, median (IQR)		7.23 (16.80)	
Previous flares ^a , median (IQR)	2.5 (3)		
SLEDAI, mean ± SD	14.3 ± 5.4	2.7 ± 1.7	< 0.001
SLICC > 0, n (%)	10 (19.2)	14 (26.9)	0.125
Immunological and serological features			
Positive anti-dsDNA antibodies ^b , n (%)	44 (88.0)	40 (80.0)	0.219
C3 complement level, median (IQR)	68.00 (45)	96.00 (17)	< 0.001
C4 complement level, mean ± SD	9.24 ± 5.41	15.24 ± 6.86	< 0.001
CH50 complement level, mean ± SD	26.16 ± 18.26	42.25 ± 11.64	< 0.001
Atherosclerosis-related variables			
Hypertension ^c , n (%)	17 (32.7)	18 (34.6)	1.000
Current smoker, n (%)	11 (21.2)	6 (11.5)	0.125
Creatinine clearance < 60 ml/min/1.73 m ² , n (%) ^d	8 (16.3)	10 (20.4)	0.625
Regicor ^e , % 10-year risk, mean ± SD	1.69 ± 0.95	1.67 ± 1.00	0.910
Dorica ^e , % 10-year risk, mean ± SD	1.96 ± 1.70	1.75 ± 1.60	0.480
Menopause, n (%)	6 (11.5)	6 (11.5)	1.000
Diabetes, coronary heart disease, or stroke	0 (0.0)	0 (0.0)	1.000
Clinical symptomatology ^f			
Renal ^g , n (%)	35 (67.3)	6 (11.5)	< 0.001
Neurological, n (%)	2 (3.8)	0 (0.0)	0.500
Musculoskeletal (arthritis or myositis), n (%)	24 (46.2)	0 (0.0)	< 0.001
Serositis, n (%)	11 (21.2)	0 (0.0)	0.001
Mucocutaneous, n (%)	23 (44.2)	1 (1.9)	< 0.001
Treatment			
No treatment for SLE ^h , n (%)	2 (3.8)	0 (0.0)	0.500
Started corticosteroids to treat flare ^j , n (%)	21 (40.4)		
Prednisone dose, mg/day ^k , median (IQR)	8.8 (15.0)	5 (2.5)	< 0.001
Prednisone dose > 10 mg/day, n (%)	22 (42.3)	2 (3.8)	< 0.001
Accumulated dose of prednisone from diagnosis, mg, median (IQR)	13,770 (28,414)	20,574 (26,558)	< 0.001
Antimalarials, n (%)	26 (50.0)	21 (40.4)	0.302
Immunosuppressive agents, n (%)	20 (38.5)	43 (82.7)	< 0.001
Methotrexate/leflunomide, n (%)	5 (9.6)	8 (15.4)	0.549
Cyclosporine/tacrolimus, n (%)	4 (7.7)	14 (26.9)	0.002
Mycophenolate/azathioprine, n (%)	11 (21.2)	34 (65.4)	< 0.001
Cyclophosphamide, n (%)	0 (0.0)	1 (1.9)	1.000

^a Any flare (including current flare) with SLEDAI ≥ 6 was considered. ^b Anti-double-stranded DNA antibodies above normal range for testing laboratory. ^c Systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mm Hg 3 separate times and/or when patient was receiving antihypertensive drugs. ^d Estimated with Modification of Diet in Renal Disease. ^e Adaptations of the Framingham scale according to prevalence of independent risk factors and incidence of coronary events in Catalan and Spanish population, respectively, to estimate 10-year global risk of coronary heart disease. Score < 5% confers low risk. ^f Disease activity events were restricted to those of SLEDAI scores. ^g Patients with proteinuria as new onset (> 0.5 g/24 h) or recent increase > 0.5 g/24 h. During remission all proteinuria values were lower than flare but higher than recent previous measure; ^h At time of sampling patient was not taking immunosuppressive agents, corticosteroids, or antimalarials. ⁱ Blood sample was taken after modifying or introducing corticosteroid doses (we did not accept any patient with recent changes in immunosuppressive therapy). ^k Prednisone or equivalent (mg/day) at time of blood-sampling.

($p = 0.010$ and $p = 0.031$), and mycophenolate/azathioprine treatment during remission ($p = 0.006$ and $p = 0.024$, respectively). Adjusting by clearance in remission at < 60 ml/min/1.73 m² we found that the statistical significance disappeared. Thus, we analyzed changes in the TC/HDL and LDL/HDL ratios between flare and remission in this group of patients with clearance in remission of < 60 ml/min/1.73 m², and observed no statistically significant differences (4.7 ± 1.0 vs 4.9 ± 1.0 , $p = 0.236$; and 3.0 ± 0.7 vs 3.2 ± 0.8 , $p = 0.270$, respectively). In the group of

patients with clearance during remission ≥ 60 ml/min/1.73 m², statistically significant differences were still observed (4.9 ± 1.7 vs 3.7 ± 0.9 , $p = 0.002$; and 2.7 ± 1.2 vs 2.2 ± 0.7 , $p = 0.006$, respectively).

Lipid risk levels. We calculated the percentage of lipid profile values that diverged from optimal levels during flare and during remission (Table 3). Although the percentage of lipid profile values that diverged from optimal levels was higher during flare than during remission for all measures, none achieved statistical significance (data not shown). When we

Table 2. Lipid profile: measures and differences between flare and remission.

Lipid Profile	Flare	Remission	p
Total cholesterol, mmol/l, mean ± SD	5.44 ± 1.40	5.15 ± 1.08	0.110
HDLC, mmol/l, mean ± SD	1.33 ± 0.49	1.37 ± 0.40	0.491
LDLC, mmol/l, mean ± SD	3.33 ± 1.19	3.13 ± 0.84	0.149
Triglycerides, mmol/l, median (IQR)	1.41 (0.99)	1.29 (1.00)	0.090
TC/HDLC ratio, mean ± SD	4.5 ± 1.5	3.9 ± 1.0	0.007
LDLC/HDLC ratio, mean ± SD	2.7 ± 1.1	2.4 ± 0.8	0.015

HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; TC: total cholesterol.

Table 3. Percentages of SLE patients in flare and remission that diverged from the desirable levels for each value of lipid profile, and percentage of patients changing high-risk levels during flare to desirable levels in remission, and vice versa. p value compares these latter changes.

Lipid Profile	Flare	Remission	Changing from Risky to Desirable Levels	Changing from Desirable to Risky Levels	p (McNemar)
Total cholesterol ≥ 5.17 mmol/l, n (%)	28 (53.8)	24 (46.2)	8 (15.4)	4 (7.7)	0.388
HDLC < 1.03 mmol/l, n (%)	15 (28.8)	10 (19.2)	6 (11.5)	1 (1.9)	0.125
LDLC ≥ 3.36 mmol/l, n (%)	22 (42.3)	19 (37.3)	9 (17.6)	6 (11.8)	0.607
Triglycerides ≥ 1.64 mmol/l, n (%)	21 (40.4)	17 (32.7)	9 (17.6)	6 (11.8)	0.607
TC/HDLC ratio, n (%)*	20 (38.5)	14 (26.9)	11 (21.2)	5 (9.6)	0.210
LDLC/HDLC ratio, n (%)**	17 (34.7)	9 (18.4)	9 (19.1)	1 (2.1)	0.021

* ≤ 5 in men, ≤ 4.5 in women. ** ≤ 3.5 in men, ≤ 3 in women. HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; TC: total cholesterol.

analyzed the variation from risk levels during flare compared to optimal values during remission and vice versa, we found that LDLC/HDLC ratio had a statistically significant variation. Nine patients diverged from optimal values during flare and changed to optimal values in remission, and only 1 patient had optimal values during flare and changed to undesirable values during remission.

The same results, statistically significant changes of only the LDLC/HDLC ratio, were observed when we analyzed patients grouped according to clearance during remission ≥ 60 ml/min/1.73 m² and after excluding menopausal women (p = 0.039 in both analyses). However, when we analyzed only patients with clearance in remission < 60 ml/min/1.73 m², there was no statistically significant change in any lipid profile variable.

During flare, 40 out of 52 patients (76.9%) had at least one lipid profile value higher than optimal levels. During remission 37 of 52 patients (71.2%) had at least one lipid profile value higher than optimal levels. Both percentages of at least one lipid profile value higher than the desirable levels were the same at flare and at remission (p = 0.502).

Only 2 patients in our study were receiving statin therapy at flare; thus, it was not possible to analyze the specific effects of statins on lipids, and the effect of this medication was considered negligible.

Other analysis. We examined the association between lipid levels during flare and during remission and serological and immunological features. We found that levels of anti-dsDNA antibodies correlated with several levels of lipid

values, during flare (HDLC $r_s = -0.395$, p = 0.004; TC/HDLC ratio $r_s = 0.365$, p = 0.008; LDLC/HDLC ratio $r_s = 0.330$, p = 0.022) and during remission (HDLC $r_s = -0.307$, p = 0.028; TC/HDLC ratio $r_s = 0.280$, p = 0.046). Values of C3 correlated with several levels of lipid values during flare (HDLC r = 0.308, p = 0.026; triglycerides $r_s = -0.341$, p = 0.013; TC/HDLC ratio r = -0.404, p = 0.003; LDLC/HDLC ratio r = -0.362, p = 0.011) and the same outcome was found for CH50 (triglycerides $r_s = -0.317$, p = 0.034; TC/HDLC ratio r = -0.352, p = 0.018). Values of fibrinogen correlated negatively with both ratios only during remission (TC/HDLC ratio r = -0.305, p = 0.028; LDLC/HDLC ratio r = -0.326, p = 0.021).

DISCUSSION

SLE is associated with an increased risk of atherosclerosis. To our knowledge, our data are the first taking serial samples to analyze levels of lipid profiles from the same adult patient with SLE at 2 different periods of disease — flare and remission. We believe this is the first such prospective study in SLE patients. Previously, Sarkissian, *et al* published 2 retrospective studies^{10,11}, limited to pediatric patients. Both described the same sample of patients, and differed in the way patients were grouped in the statistical methods and the conclusions achieved.

We observed no statistically significant differences between flare and remission in absolute values of the lipid profiles (although we observed a tendency to worsening of all the lipid profile values during flare compared with values

during remission). Only TC/HDLC and LDLC/HDLC ratios were higher at flare than at remission. Therefore, according to previous studies^{9,10,22-27}, the lipid profile worsened during flare. Indeed, we observed that several lipid profile values showed correlation with serological and immunological markers of disease activity.

Many studies have confirmed that TC/HDLC and LDLC/HDLC ratios are potent predictors of coronary risk, and this predictive power is maintained for any serum level of TC in both men and women of all ages, being a more powerful predictor of coronary risk than serum levels of TC, LDLC, or HDLC considered independently²⁸⁻³².

Data from large observational³³⁻³⁵ and angiographic studies suggest that the TC/HDLC ratio is a more powerful predictor of coronary risk than serum levels of TC, LDLC, or HDLC used independently, being a reliable discriminator of the presence and extent of CHD in women³⁶⁻³⁸. The TC/HDLC index has been considered by some investigators²⁹ a better coronary risk predictor than LDLC/HDLC because the former includes all apoB-containing lipoproteins in the numerator and not only LDL. It has recently been described in a large metaanalysis³⁹ that the TC/HDLC ratio is the strongest predictor of CHD. For the TC/HDLC ratio there were strong positive associations with CHD mortality at all ages, with no evidence of thresholds (within the range 3.7 to 7.0) beyond which higher TC/HDLC ratio was no longer associated with higher CHD mortality. Hence, a higher index implies an increased cardiovascular risk, and lowering this ratio has been shown to decrease this risk — for example, lowering this ratio from 6.0 to 4.5 halves the 5-year rate of coronary disease in women⁴⁰. Therefore, we may assume that our patients with higher values of TC/HDLC ratio during flare than during remission had increased cardiovascular risk during flare.

A study is needed to determine a possible association between LDLC/HDLC ratio and mortality due to CHD. Consequently, despite the higher values during flare than during remission, we cannot conclude that this increase would mean an increase of CHD risk. However, we found that there were a statistically significant number of patients with a pathological LDLC/HDLC ratio during flare that changed to desirable values during remission, compared to the other way around. Consequently, we may assume that our patients with pathological HDLC/LDLC ratios during flare that changed to desirable values in remission had increased cardiovascular risk during flare.

The same phenomenon described in our survey with regard to lipid values has been observed in patients with early rheumatoid arthritis (another disease associated with excess cardiovascular morbidity and mortality). In a study in the same patients (under treatment and after achieving response criteria), a significant reduction was observed of the atherogenic TC/HDLC ratio⁴¹ and the LDLC/HDLC ratio⁴¹. However, in SLE these ratios, representing athero-

genic indexes of important prognostic markers for cardiovascular disease, have been underevaluated^{7,10,22,26,42}. Blood levels of TC and other lipid fractions have been used widely to predict CHD in patients with SLE, but there are few studies evaluating the ratios in such patients^{7,43,44}.

We chose to evaluate the influence of renal flare^{7,10,42,45}, creatinine clearance⁴⁶, prednisone doses^{3,6-8,10,11,25,44,47-49}, and antimalarial treatment^{47,50} on the change of values of the 2 ratios during flare and during remission because previous studies have shown that these variables are related to lipid profile in SLE. Since we observed a higher percentage of patients receiving immunosuppressive agents during remission, we also evaluated the influence of their use on the change of both ratios during flare and remission. The study revealed that changes in levels of ratios were mainly associated with changes in disease activity. The significant changes of both ratios between flare and remission that we found were influenced only by a clearance of creatinine in remission of less than 60 ml/min/1.73 m². The ratios in these patients did not change between flare and remission, and there were no statistically significant changes in the percentage of patients that changed from undesirable values during flare to desirable values during remission, and vice versa. In these patients, renal disease was found to be the main influence on lipid profile, not changing in relation with disease activity. These findings are consistent with other studies showing the relation between nephropathy and lipid profile in SLE^{7,10,42,45}.

Considering the utility of the 2 lipid ratios in our study, we would recommend measurement of atherogenic ratios in all SLE patients to evaluate cardiovascular risk. Our results are in accord with accumulating evidence of the intriguing interactions among dyslipidemia, atherosclerosis, and inflammation, showing a worsening of the lipid profile during increased disease activity. Given the increasing recognition of coronary heart disease as an important morbidity and mortality outcome in patients with SLE, our data would support aggressive primary prevention of coronary heart disease based on treatment to avoid flares and to treat patients with an adverse lipid profile more intensively.

ACKNOWLEDGMENT

We thank Dr. Xavier Pintó for review of the manuscript.

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