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Dysfunctional Pro-Inflammatory High Density Lipoproteins Confer Increased Risk for Atherosclerosis in Women with Systemic Lupus Erythematosus

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Abstract

Objective—Women with systemic lupus erythematosus (SLE) have increased atherosclerosis. Identification of at-risk patients and the etiology underlying atherosclerosis in SLE remains elusive. Normal HDL lose antioxidant capacity during inflammation, and these dysfunctional HDL might predispose to atherosclerosis. The aim of this study is to determine whether dysfunctional pro-inflammatory HDL (piHDL) is associated with subclinical atherosclerosis in SLE.

Methods—276 SLE women had carotid artery ultrasound to identify plaques and measure intima-media thickness (IMT). Antioxidant function of HDL was measured as change in oxidation of LDL after addition of subject HDL. Two anti-inflammatory HDL components, paraoxonase and apolipoprotein A-1, were also measured.

Results—48.2% of patients had piHDL. 86.7% of subjects with plaque had piHDL, versus 40.7% without ($p<0.001$). Patients with piHDL also had higher IMT ($p<0.001$). After multivariate analysis, the only significant factors associated with plaque were piHDL, (OR 16.1, $p<0.001$), age (OR 1.2, $p<0.001$), hypertension (OR 3.0, $p=0.04$), dyslipidemia (OR 3.4, $p=0.04$), and mixed racial background (OR 8.3, $p=0.04$). Factors associated with IMT measurements in the highest quartile were piHDL (OR 2.5, $p=0.02$), age (OR 1.1, $p<0.001$), body mass index (OR 1.07, $p=0.04$), lifetime prednisone dose > 20g (OR 2.8, $p=0.04$), and African American race (OR 8.3, $p=0.001$).

Conclusions—Dysfunctional piHDL greatly increases risk for subclinical atherosclerosis in SLE; they associate with increased prevalence of carotid plaque and with high IMT. The presence of piHDL may help identify patients at risk for atherosclerosis.

Premature atherosclerosis is a major co-morbid condition in systemic lupus erythematosus (SLE), with a 10 to 50-fold increased risk of myocardial infarction (MI) (1,2). Women with SLE also have increased subclinical atherosclerosis, measured by plaque on carotid ultrasound (3,4) or calcification in coronary arteries (5,6). Traditional cardiac risk factors

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explain some of this increase (2,7), but there is still up to a 10-fold increased risk for MI after controlling for traditional factors (2). Thus, standard measures alone cannot reliably predict which SLE patients are at risk for cardiovascular morbidity.

Plasma levels of high density lipoprotein (HDL-C) are inversely related to cardiovascular disease in the general population (8). This relationship is actually quite complex and involves not only quantity but also function of HDL-C (9). Total HDL-C, a group of particles of varying size and content, is anti-inflammatory in the basal state through at least two mechanisms. First, normal HDL prevents oxidation of low density lipoprotein (LDL-C) and thus reduces the ability of oxidized LDL to attract monocytes into arterial tissue, where they form foam cells (10). These antioxidant effects depend in large part on HDL content of apolipoprotein A-1 (apoA-1) and of the enzyme paraoxonase (PON1) (10). During acute-phase responses, HDL lose this anti-oxidant capacity and can even promote increased oxidation of LDL, thus becoming pro-inflammatory (10-12). Secondly, normal HDL-C mediate reverse cholesterol transport, removing cholesterol from artery walls (10). We hypothesized that the chronic inflammation of SLE may continually promote conversion of HDL-C into a pro-oxidant, and thus pro-inflammatory state, thereby increasing risk for atherosclerosis. Supporting this hypothesis, we previously reported that HDL function is abnormal and pro-inflammatory in 45% of women with SLE, compared to 20% with rheumatoid arthritis (RA) and 4% of healthy controls. The odds ratio for having piHDL in SLE compared to healthy controls was 19.3 (95% C.I. 4.4 – 85.3). The present study was undertaken to determine if the presence of dysfunctional, pro-oxidant, and pro-inflammatory HDL (piHDL) predicts subclinical atherosclerosis in women with SLE.

Patients and Methods

Study population

281 SLE patients were enrolled between February 2004 and November 2008. All subjects are seen in the Rheumatology Practices of the University of California Los Angeles (UCLA) or Cedars Sinai Medical Center in Los Angeles. They fulfilled at least four of the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE (13). Because statins are known to alter HDL inflammatory function (9), subjects were excluded if they had taken statins within the prior three months, or if they had renal failure (defined as Cr > 2.0), which also alters HDL function (14). Five subjects who completed all study procedures were found on chart review to be taking statins and were removed from the final analysis. After exclusions, the final group consisted of 276 SLE patients. Clinical data relevant to SLE, cardiovascular disease events and risk, and ethnicity are shown in Tables 1 and 2. The definitions used for cardiac risk factors such as hypertension, diabetes, family history of cardiac disease, etc., are also given in Table 1. This study was approved by the Institutional Review Boards at UCLA and Cedars-Sinai Medical Center; all participants gave written informed consent.

Sample collection

Blood samples were processed with sucrose cryopreservation; HDL-C was isolated from plasma using a magnetic bead Dextran Sulfate reagent (Reference Diagnostics, Bedford, MA) as previously described (9). Plasma lipid concentrations, levels of high sensitivity CRP (hs-CRP) and serum complement, erythrocyte sedimentation rate (ESR), and autoantibodies against DNA and cardiolipin were measured in the UCLA clinical laboratory using standard methods. On the day of plasma sampling, the disease activity of SLE subjects was assessed using the SELENA-SLEDAI validated instrument (15). Organ damage was determined using the Systemic Lupus International Collaborating Clinics / ACR damage index (SDI) (16). Cumulative lifetime prednisone doses were calculated by chart review.

Carotid Ultrasound

B (brightness)-mode grey scale, color and spectral Doppler techniques were used to investigate the carotid arteries according to a standardized protocol (17). The same radiologist (NR) interpreted all studies in a blinded fashion, and the same ultrasound unit (Iu22, Philips Medical Systems, Bothell, WA) was used for scanning all participants.

The following anatomical sites were examined for the presence of atherosclerotic plaque, defined as the presence of focal protrusion (intima-media thickening) into the arterial lumen with a thickness exceeding that of the surrounding wall by at least 50%: the bilateral common carotid arteries, the carotid bulbs, the bilateral internal carotid arteries, the bilateral external carotid arteries, and the bilateral vertebral arteries. The number, location and sonographic appearance of the plaques were recorded. Intima-media thickness (IMT) of the far wall of the distal common carotid artery was measured (a) 1 cm proximal to the flow divider, (b) at end diastole on cineloop real-time playback, and (c) using automated QLAB software (Philips Medical Systems, Bothell, WA). IMT was never measured at the level of a plaque and is presented as the average of three values of the left and right segments.

Cell-free Assay for Measurement of HDL-C function

Dysfunctional HDL has historically been diagnosed using a cell-based assay that requires endothelial cells, smooth muscle cells, and monocytes; however, this assay is not practical for large-scale studies (18). A cell-free assay has been developed that rapidly detects dysfunctional HDL and gives results that are highly comparable to the cell based-assay (9,19). The assay is based on the ability of normal HDL to prevent oxidation of LDL. The presence of oxidized LDL leads to the conversion of normally non-fluorescent dichlorofluorescein diacetate (DCFH-DA) into a fluorescent form (DCFH). DCFH is then measured on a plate reader (Spectra Max, Gemini XS; Molecular Devices, Sunnyvale, CA) set at an excitation wavelength of 485 nm and an emission wavelength of 530 nm, and the change in fluorescence intensity resulting from oxidation of DCFH-DA by LDL in the presence or absence of test HDL can be quantitated. Dysfunctional HDL is unable to prevent the oxidation of LDL that occurs spontaneously in vitro, and actually increases oxidation, and thus can be considered pro-oxidant and pro-inflammatory. LDL-C was prepared from normal plasma as previously described (19). 20 μL of the normal LDL-C solution (final concentration of 50 μg/ml) and 90 μL of test HDL-C (at a final concentration of 10 μg/mL cholesterol) were incubated in quadruplicate in 96-well plates for one hour. 10 μL of DCFH-DA solution (0.2mg/mL) were added to each well and incubated for 2 hours. Fluorescence was then determined with a plate reader. Values of DCFH activated by LDL-C alone were normalized to 1.0. In addition to preventing the oxidation of LDL, the presence of dysfunctional HDL in the assay often amplified LDL oxidation and subsequent DCF formation. Therefore, values equal to or greater than 1.0 after the addition of test HDL-C indicated dysfunctional, pro-inflammatory HDL; values less than 1.0 indicated normal, anti-inflammatory HDL.

Measurement of apoA-1 and Paraoxonase Activity

Plasma paraoxonase (PON1) activity was measured using paraoxon as a substrate according to the previously described method by Eckerson et al. (20). ApoA-1 levels were measured using ELISA (Mabtech, Cincinnati, OH).

Statistical Analysis

Data were analyzed using SPSS 13.0 (SPSS, Inc, Chicago, IL 2005). Skewed continuous variables were logarithmically transformed to attain a normal distribution. For variables that did not attain a normal distribution by logarithmic transformation, nonparametric tests were

used. Study groups were compared using analysis of variance / student's t-test for continuous parametric variables, Mann-Whitney test for non-parametric variables, and the chi-square test for categorical variables. Either Pearson or Spearman rank correlation was calculated, dependent on if the variable was normally distributed. The significance level was set at $P < 0.05$. Multiple regression analysis was used to build models identifying risk factors associated with the presence of plaque and highest quartile of IMT in SLE subjects.

Results

Plaque is Associated with Some Traditional Cardiac and SLE-Disease Specific Risk Factors

Forty-five of 276 (16.3%) subjects in the SLE group had ≥ 1 area of plaque on carotid ultrasound. In univariate analysis, SLE patients with plaque were more likely to have hypertension (defined as present or not present) ($p<0.001$), a higher mean systolic blood pressure at time of study entry (continuous variable, $p=0.02$), diabetes (defined as present or not present)($p=0.004$), a previous history of documented coronary artery disease ($p=0.04$), a family history of cardiovascular disease ($p<0.001$), older age (continuous) ($p<0.001$), higher total cholesterol levels ($p<0.001$), higher LDL-C levels ($p<0.001$), and a higher body mass index ($p=0.05$). They were also more likely to have the presence of any dyslipidemia on the blood draw at study entry (defined as LDL cholesterol ≥ 130mg/dL, Total cholesterol ≥ 200 mg/dL, HDL cholesterol ≤ 40mg/dL, triglycerides ≥ 150 mg/dL) ($p<0.001$). In addition, patients of African American descent were also more likely to have plaque. There were no associations between the presence of plaque and a history of smoking (now or ever), or a prior documented history of cerebrovascular disease. There were also no associations between the presence of plaque and levels of HDL-C, triglycerides, or hs-CRP (Table 1).

Relationships between carotid plaque and disease activity or damage were also examined in SLE subjects. Higher SDI was positively associated with plaque ($p=0.01$), as was longer disease duration ($p=0.002$). However, plaque was not associated significantly with previous renal disease or renal transplant, active renal disease, a history of documented positive antiphospholipid antibodies, SELENA-SLEDAI score at the time of blood sampling, or any current SLE-related medications, including current use of prednisone, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, non-steroidal anti-inflammatories, or 6-month cumulative prednisone dose (Table 2).

IMT in SLE patients is associated with some traditional cardiac risk factors

The mean IMT in the group was 0.55 ± 0.14 mm^2. The relationships between cardiac risk factors and IMT measurements in the highest quartile (≥ $0.65mm^2$) compared to the lowest three quartiles were determined in SLE subjects using bivariate analysis. Subjects in the highest quartile of IMT measurements were more likely to have hypertension ($p<0.001$), older age, ($p<0.001$), higher body mass index ($p<0.001$), higher total cholesterol ($p<0.001$) and higher LDL cholesterol ($p<0.001$). They were also more likely to have any dyslipidemia on study blood draw ($p<0.001$), to have a history of previous coronary artery disease, and to be of African American descent ($p<0.001$). In addition, SLE patients in the highest quartile of IMT were more likely to have longer disease duration ($p=0.001$), to have a cumulative lifetime prednisone dose greater than 20 grams ($p=0.04$), and to have a higher mean SDI ($p=0.01$); they were less likely to have a past history of glomerulonephritis ($p=0.04$), and were also less likely to be taking hydroxychloroquine ($p=0.002$). There were no associations between the highest quartile of IMT and current or past tobacco use, a family history of cardiovascular disease, a history of diabetes, a history previous cerebrovascular disease, hs-CRP, HDL-C, triglycerides, SELENA-SLEDAI at the time of the study blood draw, or history of past or current antiphospholipid antibodies (Table 3). There were also no

associations with any other current SLE-related medications, including current use of prednisone, cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, non-steroidal anti-inflammatories, or 6-month cumulative prednisone dose (data not shown).

Pro-Inflammatory HDL is Strongly Associated with Subclinical Atherosclerosis, both Plaque and IMT, in SLE patients

The mean HDL function of the entire SLE cohort was pro-inflammatory, with a score of 1.09 ± 0.67 (mean ± S.D.). Using a HDL function score of ≥ 1.0 to define pro-inflammatory HDL, 48.2% of SLE patients had piHDL. These results are similar to our previously published cohort, in which the mean HDL function score was 1.02 ± 0.57 in SLE subjects vs. 0.68 ± 0.28 ($p<0.001$) in controls, and piHDL was found in 44% of SLE subjects (21). Among the 45 subjects in our current cohort with plaque, 39 (86.7%) had piHDL, compared to 94 of 231 (40.7%) of SLE patients without plaque ($p<0.001$) (Figure 1). Subjects with piHDL also had a higher mean number of plaques (0.62 ± 1.2 vs. 0.10 ± 0.49, $p<0.001$) than those with normal HDL function. Mean IMT was also significantly thicker in SLE subjects with piHDL (0.57 ± 0.15) than in those with normal functioning HDL (0.53 ± 0.12)($p=0.001$). Overall, the positive predictive value of a single positive piHDL test for the presence of carotid plaque was only 29.3%. However, the negative predictive value of a single positive piHDL test for carotid plaque in SLE was 95.8%.

The association between piHDL function and plaque is not explained by selected individual protective components of HDL

We tested for associations between piHDL or subclinical atherosclerosis and plasma levels of apoA-1 or activity of paraoxonase, two known protective components of normal HDL. No associations were found between PON activity or plasma levels of apoA-1 and the presence of plaque in SLE patients. There was an inverse correlation between IMT and paraoxonase activity ($r=-0.32$, $p=0.001$), but no correlation between IMT and ApoA-1 levels. Also, there was no correlation between HDL function and levels of either PON activity or apo A-1.

piHDL is Associated with Atherosclerosis in SLE Even After Accounting for Traditional Cardiac and Disease Risk Factors

Multivariate analysis determined which variables were most consistently associated with carotid plaque in SLE subjects. The model included traditional cardiac risk factors and SLE associated factors that might affect risk for cardiac disease. The significant factors were presence of piHDL (odds ratio 16.1; 95% C.I. 4.3 – 59.6, $p<0.001$), age (odds ratio 1.15; 95% C.I. 1.08 – 1.2, $p<0.001$), hypertension (odds ratio 3.0; 95% C.I. 1.05 – 8.8, $p<0.001$), dyslipidemia (odds ratio 3.4, 95% C.I. 1.06 – 10.7, $p=0.03$), and mixed racial background (odds ratio 8.3, 95% C.I. 1.2 – 59.7)(Table 4).

Using multivariate analysis for factors significantly associated with increased IMT, SLE patients in the highest quartile of average IMT (values greater than 0.65mm^2) were compared to those in the lower three quartiles (Table 5). The factors significantly associated with high IMT were piHDL, with an odds ratio of 2.5 (95% C.I. 1.1 – 5.4, $p=0.02$), older age (odds ratio 1.1, 95% C.I. 1.07 – 1.2, $p<0.001$), BMI (odds ratio 1.07, 95% C.I. 1.01 – 1.1, $p=0.04$), lifetime prednisone use greater than 20 grams (odds ratio 2.9, 95% C.I. 1.07 – 7.6, $p=0.04$), and African American racial background (odds ratio 8.3, 95% C.I. 2.4 – 28.9) (Table 5).

Discussion

SLE is associated with an increased risk of subclinical and clinical atherosclerosis (1-3), although the biological mechanisms underlying this risk are not well understood. Data presented here describe pro-inflammatory HDL as a risk factor for subclinical atherosclerosis on carotid ultrasound, manifested as increases in both the frequency of plaque and high IMT. There was no association in our cohort between quantitative HDL levels and either plaque or IMT. Furthermore, quantitative HDL levels were not associated with HDL function in either this cohort (data not shown) or in our previously published cohort of patients (21), highlighting that biological HDL function, not simply quantity, confer risk in SLE. In agreement with this concept, higher levels of “dysfunctional” HDL have been demonstrated in a cohort of patients with known cardiovascular disease, (9) as well as in patients with both inactive and active Crohn's disease when compared to healthy controls (22). In addition, dysfunctional HDL were associated with increased IMT in a small cohort of South Asian immigrants to the US, even after adjusting for quantitative HDL level, age, family history of cardiac disease, and hypertension (23).

Normal functioning HDL-C has several anti-atherogenic properties. HDL transports excess cholesterol from cells in artery walls to the liver for disposal (10,24), removes reactive oxygen species from OxLDL, prevents OxLDL-mediated recruitment of inflammatory mediators and monocytes into the vessel wall (25), and inhibits endothelial cell expression of adhesion molecules (26) and release of chemokines/cytokines (27). Several components of HDL contribute to these protective effects, including apoA-1 and the enzyme paraoxonase (28).

Conversely, piHDL cannot prevent oxidation of LDL-C and actually increase it, leading to impairment of reverse cholesterol transport, increased recruitment of monocytes, and probably an enhanced inflammatory response (11,19). Multiple mechanisms confer pro-inflammatory characteristics on HDL molecules (29). In acute inflammation, hepatic synthesis of the protective lipoproteins in HDL-C, including apoA-1 and antioxidant enzymes such as PON1, decrease (28). Additionally, protective components in the HDL particles, such as apoA-1, are partly replaced with pro-oxidant acute phase reactants such as serum amyloid A and ceruloplasmin (29) (30). Furthermore, HDL-C and apoA-1 can be readily oxidized during periods of inflammation by myeloperoxidase, a product of white blood cell activation (30); oxidation of HDL probably contributes to its dysfunction. Oxidized HDL has pro-inflammatory characteristics (29,30), and upregulates the expression of pro-inflammatory genes such as cyclo-oxygenase-2 (31) and plasminogen activator inhibitor-1 (32) in endothelial cells.

Previous studies in SLE subjects have described alterations in some protective components of HDL, including decreased PON enzymatic activity (33) (34) and decreased apoA-1 levels (35). Our data show that piHDL is a better predictor of subclinical atherosclerosis than either apoA-1 or PON1 activity. Decreased PON1 activity correlated with higher IMT, but not with plaque, in univariate but not multivariate analysis (data not shown). This is similar to data described in a group of subjects with metabolic syndrome who had more pro-inflammatory HDL than dyslipidemic controls, despite similar levels of HDL-C and PON activity (36). Interestingly, there was no association in either this cohort or our previously published cohort (21) between pro-inflammatory HDL function and traditional markers of disease activity and inflammation such as hs-CRP or SELENA-SLEDAI (data not shown).

Although high quantities of HDL cholesterol have been regarded as a negative risk factor for atherosclerosis, there is increasing evidence that HDL *function* may be as important as quantity for atheroprotection (28). This was highlighted recently by the failure of the

experimental drug torcetrapib, a cholesterol ester transfer protein (CETP) inhibitor that increases quantitative levels of HDL-C, to protect from coronary artery disease (32-34). It has been suggested that CETP inhibition results in dysfunctional pro-inflammatory HDL-C (37). Evidence from other groups also suggests that abnormal HDL function can contribute to excess mortality. In hemodialysis patients, piHDL was associated with a 2.5-fold increased risk of mortality over a 30-month period (14). It is not clear if the HDL function abnormalities described with hemodialysis are similar to those in patients with piHDL in SLE; however, the results presented here highlight the importance of HDL function in addition to quantity in the prevention of atherosclerosis in the general population. In patients with SLE, abnormal function of HDL seems more important that quantities of HDL in influencing excess risk for atherosclerosis.

Our study has some limitations. Our study population differs from previously published SLE cohorts (3,38) in that the prevalence of plaque in our SLE study group was lower than in previously published cohorts. Possible explanations include exclusion from our study of individuals taking statins (which biased towards patients without known hyperlipidemia and/or clinical atherosclerosis (9)) and inclusion of a higher proportion of Asians, who may have a lower prevalence of subclinical atherosclerosis than other racial groups (39,40). It is also possible that the SLE population in Los Angeles differs significantly from patients in other geographic areas, not only in ethnicities but also in habits such as physical exercise (41), years of protection from public smoking (42), and in hours of exposure to sunlight with influences on Vitamin D levels (43). The fact that cohorts from different centers thousands of miles apart differ in prevalence of plaque is not surprising given the differences in geography, climate, ethnic mix, behaviors, diet, exercise and the many other factors that influence health.

Another limitation of our study is that we did not measure all potential atherosclerosis biomarkers. Most notably, since the inception of our study, several groups have demonstrated an association between high homocysteine levels and subclinical atherosclerosis in SLE (6,44) (45). Future studies in our cohort will determine whether homocysteine and piHDL are independent predictors of atherosclerosis, or whether synergy exists between them.

For practical reasons, our study focused on the association between piHDL and subclinical atherosclerosis. There are currently no published studies that specifically demonstrate that lupus patients with carotid plaque or increased IMT have an elevated risk for cardiovascular events, and it is possible that these are not valid measures in women with lupus. Multiple large cohort studies, however, that have demonstrated the predictive power of these measures in the general population (46). Further longitudinal studies are needed to establish the predictive power of carotid plaque and IMT in women with SLE, and also to determine whether the presence of piHDL can predict future cardiovascular events in these patients.

In summary, piHDL contribute to a 17-fold increased odds for presence of atherosclerosis in female SLE patients. With a negative predictive value of 96%, piHDL may be one effective biomarker to determine which SLE patients are at low risk for subclinical atherosclerosis. These data also suggest that further studies are needed to determine whether interventions that restore protective anti-inflammatory functions of HDL-C, including statins (9), exercise and diet (47), and/or treatment with apo-AI mimetic peptides (48), will be useful to prevent atherosclerosis in patients with SLE.

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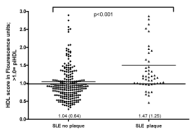

Figure 1. Distribution of HDL function scores in SLE patients with or without plaque

Each dot represents individual patient HDL function scores. The horizontal line at 1.0 indicates the dividing line for abnormal, pro-inflammatory HDL scores (≥1.0 is pro-inflammatory). The heavy horizontal black lines in each column indicate mean scores.

Table 1

Demographic and baseline cardiac risk data on SLE patients with and without plaque

	With plaque (n=45)	Without plaque (n=231)	p-value †
Age (years) (mean ± SD)	**55.7 ± 9.5**	**39.8 ± 12.0**	**<0.001**
Total cholesterol (mg/dL) (mean ± SD)	**209.6 ± 42.4**	**180.4 ± 41.8**	**<0.001**
HDL (mg/dL) (mean ± SD)‡	57.5± 17.6	56.0 ± 16.5	ns
LDL (mg/dL) (mean ± SD)‡	**124.7 ± 37.4**	**102.2 ± 33.3**	**<0.001**
Triglycerides (mg/dL) (mean ± SD)	126.7 ± 68.7	110.3 ±71.8	ns
Presence of Dyslipidemia **	**62.2% (28)**	**26.4% (61)**	**<0.001**
History of Hypertension % *(n)*†	**60.0% (27)**	**26.4% (61)**	**<0.001**
Systolic Blood Pressure (mean ± SD)	**118.0 ± 18.1**	**112.1 ± 13.5**	**0.02**
Diastolic Blood Pressure (mean ± SD)	71.8 ± 12.4	70.9 ± 9.3	ns
History of previous CAD % *(n)**	6.7% (3)	0	0.04
History of cerebrovascular events % *(n)**	11.1% (5)	6.1% (14)	ns
High-sensitivity CRP (mg/L) (mean ± SD)	4.0 ± 7.4	2.6 ± 6.7	ns
Body Mass Index	**27.0 ± 6.5**	**24.9 ±6.9**	**0.05**
History of Diabetes % *(n)*‡	**11.1% (5)**	**3.9% (9)**	**0.04**
History of Smoking (current) % *(n)*¶	8.9% (4)	6.9% (16)	ns
History of Smoking (ever) % *(n)*	33.3% (15)	27.7% (64)	ns
Family History of CVD% *(n)* ¶¶	**35.6% (16)**	**20.3% (47)**	**0.03**
Race/Ethnicity % *(n)*			
Caucasian	46.7% (21)	49.8 % (115)	ns
Asian or Pacific Islander	8.9% (4)	13.9 % (32)	ns
African American	**26.7 % (12)**	**10.0% (23)**	**0.002**
Hispanic	8.8 % (4)	21.2 % (49)	ns
Mixed or Other ***	8.9% (4)	5.2% (12)	ns

† p-values shown only if statistically significant

‡ HDL = high density lipoprotein; LDL = low density lipoprotein.

* Coronary artery disease (CAD) was defined as a history of MI with appropriate documentation, or CAD documented on angiogram or stress test. Cerebrovascular events included transient ischemic attacks (confirmed by physician) and stroke (confirmed by appropriate imaging).

† Hypertension was defined as use of antihypertensive medication or a systolic blood pressure > 140 mg Hg or a diastolic blood pressure > 90 mm Hg.

‡ Diabetes mellitus was defined as the presence of a fasting glucose ≥ 7.0 mmoles/liter (126 mg/dl), or treatment with insulin or an oral hypoglycemicat the time of study entry;

¶ Smoking was present if subjects had smoked any cigarettes within the last 3 months.

¶¶ Family History of Cardiovascular Disease (CVD) was defined as MI, stroke, or sudden death in any first degree relative before age 60 years

** Dyslipidemia was defined as any one or combination of the following: LDL cholesterol ≥ 130mg/dL, Total cholesterol ≥ 200 mg/dL, HDL cholesterol ≤ 40mg/dL, triglycerides ≥ 150 mg/dL

*** Subjects self reported a mixture of racial/ethnic backgrounds, including: Asian/Caucasian (3), African American/Caucasian (3), Caucasian/Hispanic (5), Native American/Caucasian (1), Hispanic/Native American (2), Hispanic/African American (2)

Table 2

Disease characteristics of SLE subjects with and without plaque

	With plaque (n=45)	Without plaque (n=231)	p-value
History of glomerulonephritis (ever) % (n)	28.9% (13)	25.5% (59)	ns
Mean disease duration (years) (± SD)	**16.8 ± 10.5**	**11.4 ± 7.8**	**0.002**
Mean SELENA-SLEDAI (± SD) disease activity	**2.9 ± 3.2**	**4.2 ± 4.1**	**0.06**
Mean SDI (± SD) **	**2.0± 2.0**	**1.2± 1.6**	**0.01**
History of Lupus Anticoagulant positive % ***(n)***	6.7% (3)	15.6% (36)	ns
History of anticardiolipin antibody positive ¶¶¶ % ***(n)***	24.4% (11)	40.3% (93)	ns
Current Medications: % ***(n)***			
Mycophenolate Mofetil	20.0% (9)	22.9% (53)	ns
Hydroxychloroquine	55.6% (25)	65.8% (152)	ns
Cyclophosphamide	0% (0)	1.3% (3)	ns
Methotrexate	4.4% (2)	6.9% (16)	ns
Azathioprine	8.8% (4)	12.6% (29)	ns
Non-Steroidal Anti-Inflammatory	51.1% (23)	38.5% (89)	0.1
Current Glucocorticoid Use	44.4% (20)	45.0% (104)	ns
Mean Current Prednisone (mg) (± SD)	3.1 ± 4.5	4.8 ± 8.5	0.06
Cumulative Lifetime Prednisone dose ≥ 20g % ***(n)***	40.0% (18)	27.8% (64)	0.07

§ SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus—National Assessment (SELENA) SLE Disease Activity Index.

// SDI = Systemic Lupus Collaborating Clinics/American College of Rheumatology damage index

¶¶¶ History of anticardiolipin antibody positive includes IgG, IgM, or IgA positive on at least 2 separate occasions 6 weeks apart

Table 3

Demographic and baseline cardiac risk data on SLE patients in highest quartile IMT (≥0.65mm^2) compared to lower three quartiles

	High IMT (n=70)	Lower IMT (n=206)	p-value †
Age (years) (mean ± SD)	**54.1 ± 9.8**	**38.3 ± 11.5**	**<0.001**
Total cholesterol (mg/dL) (mean ± SD)	**201.0 ± 42.1**	**180.0 ± 42.4**	**<0.001**
HDL (mg/dL) (mean ± SD)‡	57.1± 14.9	56.0 ± 17.2	ns
LDL (mg/dL) (mean ± SD)‡	**118.6 ± 35.6**	**101.7 ± 33.8**	**<0.001**
Triglycerides (mg/dL) (mean ± SD)	126.8 ± 83.0	108.4 ±66.8	ns
Presence of Dyslipidemia % *(n)***	**45.7% (32)**	**27.6% (57)**	**<0.001**
History of Hypertension % *(n)*†	**50.0% (35)**	**25.8% (53)**	**<0.001**
History of previous CAD % ***(n)****	4.3% (3)	0% (0)	0.02
History of cerebrovascular events % ***(n)****	11.4% (8)	5.3% (11)	ns
High-sensitivity CRP (mg/L) (mean ± SD)	2.8 ± 5.5	2.9 ± 7.2	ns
Body Mass Index	**28.6 ± 6.2**	**25.3 ± 6.2**	**<0.001**
History of Diabetes % *(n)*‡	**8.6% (6)**	**3.8% (8)**	**ns**
History of Smoking (current) % ***(n)***¶	4.3% (3)	8.3% (17)	ns
Family History of CVD% *(n)* ¶¶	30% (21)	20.4% (42)	0.14
Past History of Glomerulonephritis	**17.1% (12)**	**29.1% (60)**	**0.04**
Race/Ethnicity % ***(n)***			
Caucasian	47.1% (33)	50.5 % (103)	ns
Asian or Pacific Islander	7.1% (5)	15.0 % (31)	0.1
African American	**30.0 % (21)**	**6.8% (14)**	**<0.001**
Hispanic	11.4 % (8)	21.8 % (45)	0.06
Mixed or Other	8.9% (4)	5.2% (12)	ns
Mean disease duration (years) (± SD)	**15.5 ± 9.2**	**11.1 ± 7.9**	**0.001**
Mean SELENA-SLEDAI (± SD) disease	4.1 ± 4.4	3.9 ± 3.9	ns
Mean SDI (± SD) **	**1.8± 1.8**	**1.1± 1.6**	**0.01**
History of Lupus Anticoagulant positive %	8.6% (6)	16% (33)	ns
History of anticardiolipin positive % ***(n)***	30% (21)	40.3% (83)	ns
Mean Current Prednisone (mg) (± SD)	3.6 ± 7.0	4.8 ± 8.5	ns
Lifetime Prednisone ≥ 20g % *(n)*	**40.0% (28)**	**26.2% (54)**	**0.04**
Current use of Hydroxychloroquine % *(n)*	**50% (35)**	**68.9% (142)**	**0.002**
Current use of Mycophenolate Mofetil % ***(n)***	15.7% (11)	24.8% (51)	0.11

Table 4

Logistic regression of the relationship of SLE to the presence of plaque on carotid ultrasound

Explanatory variable	Odds Ratio	95% CI †	P
Pro-inflammatory HDL (yes, no)	**16.1**	**4.3 - 59.6**	**<0.001**
Age (years)	**1.2**	**1.09 – 1.2**	**<0.001**
Hx Dyslipidemia*	**3.4**	**1.06 – 10.7**	**0.04**
Hypertension	**3.0**	**1.05 – 8.8**	**0.04**
Smoking (current)	5.5	0.8 – 36.6	0.07
SDI	0.7	0.5-1.01	0.08
Diabetes (yes, no)	1.07	0.1 – 10.4	ns
SLEDAI	0.9	0.8 – 1.06	ns
ln hs-CRP (mg/L)**	1.2	0.8 – 1.7	ns
Body Mass Index (kg/m^2)	1.00	0.97 – 1.09	ns
History past Glomerulonephritis (yes, no)	2.9	0.7 – 12.0	ns
Disease Duration (years)	1.04	0.97 – 1.1	ns
Hydroxychloroquine Use (yes, no)	0.9	0.3 – 2.7	ns
Lifetime Prednisone ≥ 20 g (yes, no)	2.4	0.7 – 8.3	ns
Family History of Cardiovascular Disease	1.5	0.5 – 4.4	ns
African American Race	3.5	0.8 – 14.9	0.09
Asian Race	2.2	0.4 – 11.6	ns
Mixed Race	**8.3**	**1.2 – 59.7**	**0.04**
Hispanic Ethnicity	0.8	0.2 – 3.8	ns

SDI= SLICC ACR Damage Index

** Note –The ln transformed hs-CRP variable was used for the analysis because of the severely skewed nature of the non-transformed variable. Goodness of fit statistics showed a better fit for the model using the ln transformed hs-CRP variable compared to the non-transformed variable. No other variables in the model required transformation.

† CI denotes confidence interval

Table 5

Logistic regression of the relationship of SLE to the highest quartile of IMT (≥ 0.65 mm^2)

Explanatory variable	Odds Ratio	95% CI †	P
piHDL (yes, no)	**2.5**	**1.1 – 5.4**	**0.02**
Age (years)	**1.1**	**1.07 – 1.2**	**<0.001**
Body Mass Index (kg/m^2)	**1.07**	**1.01 – 1.1**	**0.04**
Lifetime Prednisone >20g	**2.9**	**1.07 – 7.6**	**0.04**
Hydroxychloroquine use (yes, no)	0.5	0.2 – 1.1	0.09
Dyslipidemia	0.9	0.3 – 2.5	ns
Diabetes (yes, no)	1.5	0.3 – 9.2	ns
Hypertension (yes, no)	2.2	0.9 – 5.2	ns
Smoking (current)	0.9	0.2– 5.0	ns
ln hs-CRP (mg/L)*	0.8	0.6 – 1.09	ns
Disease Duration (years)	1.03	0.98 – 1.09	ns
SDI	0.9	0.7 – 1.2	ns
SLEDAI	1.07	0.97 – 1.2	ns
Family History Cardiovascular Disease (yes, no)	1.1	0.5 – 2.6	ns
History of past Glomerulonephritis	0.4	0.1 – 1.3	ns
African American Race	**8.3**	**2.4 – 28.9**	**0.001**
Asian Race	1.3	0.3 – 5.1	ns
Mixed Race	3.4	0.7 – 16.9	ns
Hispanic Ethnicity	0.9	0.3 – 2.9	ns

SDI= SLICC ACR Damage Index

*Note – Again, as described in table 4, the ln transformed hs-CRP variable was used for the analysis because of the severely skewed nature of the non-transformed variable.

†CI denotes confidence interval