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A Panel of Biomarkers Is Associated With Increased Risk of the Presence and Progression of Atherosclerosis in Women With Systemic Lupus Erythematosus

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Abstract

Objective—An increased frequency of atherosclerosis (ATH) in systemic lupus erythematosus (SLE) is well-documented but not fully explained by the presence of traditional cardiac risk factors. Several nontraditional biomarkers, including proinflammatory high-density lipoprotein (piHDL) and leptin, have been individually associated with subclinical ATH in SLE. The aim of this study was to examine whether these and other biomarkers can be combined into a risk profile, the Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE (PREDICTS), that could be used to better predict future progression of ATH.

Methods—In total, 210 patients with SLE and 100 age-matched healthy control subjects (all women) participated in this prospective cohort study. The longitudinal presence of carotid plaque and intima-media thickness (IMT) were measured at baseline and followup (mean ± SD 29.6 ± 9.7 months).

Results—At followup, carotid plaque was present in 29% of SLE patients. Factors significantly associated with plaque, determined using Salford Predictive Modeling and multivariate analysis, included age ≥48 years (odds ratio [OR] 4.1, $P = 0.002$), high piHDL function (OR 9.1, $P <$

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. McMahon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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0.001), leptin levels ≥34 ng/dl (OR 7.3, $P = 0.001$), plasma soluble TWEAK levels ≥373 pg/ml (OR 28.8, $P = 0.004$), and history of diabetes (OR 61.8, $P < 0.001$). Homocysteine levels ≥12 μmoles/liter were also a predictor. However, no single variable demonstrated an ideal combination of good negative predictive values (NPVs), positive predictive values (PPVs), sensitivity, and specificity. A high-risk PREDICTS profile was defined as ≥3 positive biomarkers or ≥1 positive biomarker plus a history of diabetes; for high-risk SLE patients, the PPV was 64%, NPV was 94%, sensitivity was 89%, and specificity was 79%. In multivariate analysis, SLE patients with the high-risk profile had 28-fold increased odds for the longitudinal presence of plaque ($P < 0.001$) and increased progression of IMT ($P < 0.001$).

Conclusion—A high-risk PREDICTS score confers 28-fold increased odds of the presence of any current, progressive, or acquired carotid plaque, both in patients with SLE and in control subjects, and is significantly associated with higher rates of IMT progression.

Accelerated atherosclerosis (ATH) is more common in women with systemic lupus erythematosus (SLE) compared to the general population (1). In women with SLE, ATH often occurs at a younger age (2) and causes significant morbidity and mortality (1). Traditional cardiac risk factors do not explain the high incidence of ATH in SLE (3); in multivariable analyses accounting for the presence of traditional Framingham cardiac risk factors, the odds ratio (OR) for coronary artery disease (CAD) in SLE patients is still 8–10 (2–4). Yet, despite the high risk of cardiac disease in SLE, the ideal cardiovascular prevention strategies are still unclear, as results from trials of statins in SLE patients have been disappointing (5,6). Identification of disease-related risk factors for ATH in SLE will therefore be essential for classification of high-risk subjects to allow for more effective trial designs and discovery of preventive strategies.

In a cross-sectional study by our group, proinflammatory high-density lipoprotein (piHDL) was found to be associated with the presence of plaque on carotid ultrasound images (7). Although in the general population quantitative HDL levels are inversely related to ATH (8), the relationship is complex and depends on both the quantity of HDL and its function. HDL particles are antiinflammatory in the basal state but proinflammatory during an acute-phase response (8). Chronic inflammation in SLE may therefore contribute to an increased incidence of ATH, because piHDLs fail to prevent the oxidation of low-density lipoprotein (LDL), and promote additional oxidation of LDL (9). In another study by our group, 50% of women with SLE had piHDL, as compared with fewer than 10% of age-matched healthy women (10). More strikingly, in our cross-sectional study, 87% of SLE patients with plaque on carotid ultrasound had piHDL, as compared with 41% of those without carotid plaque (7).

Plasma levels of the adipokine leptin are also significantly higher in SLE patients with plaque when compared to control subjects with plaque (11). Leptin modulates food intake and fat stores (12), and hyperleptinemia in the general population is associated with hypertension (12), oxidative stress (13), and endothelial dysfunction (14). Leptin levels are elevated in adult (15,16) and pediatric (17) SLE patients. In one cross-sectional study by our group, leptin levels were independently associated with carotid plaque and positively correlated with piHDL and oxidized phospholipids in lupus patients (11).

Several groups of investigators have identified homocysteine levels as a predictor for the development of CAD and the occurrence of stroke in the general population (18). In addition, homocysteine levels have been identified as a predictor of ATH in patients with SLE, in whom high levels may be predictive of increased levels of coronary calcium (19), plaque progression (20), and intima-media thickness (IMT) progression (21). It should be noted, however, that multiple clinical trials and a recent meta-analysis of homocysteine-lowering therapies have been unable to demonstrate a cardioprotective benefit, calling into question the relative importance of homocysteine alone in the pathogenesis of ATH (22).

The presence of soluble TWEAK (sTWEAK) is linked to increased rates of ATH, inflammation, angiogenesis, and apoptosis (23). The combination of high plasma levels of sTWEAK and high levels of interleukin-6 was associated with increased cardiovascular-related mortality and all-cause mortality in patients undergoing hemodialysis (24).

The likelihood that a single biomarker would be adequate for predicting the risk of ATH in all SLE patients is slim. We hypothesized that a combination of biomarkers and risk factors would be a better predictor for the presence and progression of atherosclerotic plaque. We therefore examined combinations of the biomarkers described above and traditional biomarkers of ATH and SLE, to develop a clinically available screening tool for the identification of SLE patients at high risk of current or future carotid plaque.

PATIENTS AND METHODS

Study population

All participants in the longitudinal cohort of the Biomarkers of Atherosclerosis in SLE study were recruited prospectively from the rheumatology practices of the University of California, Los Angeles (UCLA) and Cedars-Sinai Medical Center in Los Angeles from February 2004 to January 2010. Eligible participants were women ≥18 years of age who fulfilled ≥4 of the American College of Rheumatology (ACR) 1997 revised criteria for the classification of SLE (25). The controls were age-matched healthy women with no clinical manifestations of SLE (identified as healthy by self-report on Connective Tissue Screening Questionnaires) (26). When possible, controls were recruited using a “friend of the same age” referral strategy. When patients did not have a friend who was willing to participate, additional controls were recruited using fliers posted in the UCLA medical clinics.

Because statins (27) and renal failure (28) are known to alter HDL inflammatory function, subjects were excluded at baseline if they had received statins within the prior 3 months or if they had renal failure (defined as a serum creatinine level of >2.0 mg/dl); however, these subjects were still included in the longitudinal followup if they initiated treatment with statins or developed renal failure after the baseline ultrasound. Followup ultrasound studies were planned for 24–36 months after the baseline ultrasound; however, to minimize loss of patients to followup due to scheduling difficulties, subjects were allowed to complete a followup ultrasound at any time after 18 months from the baseline examination. In total, 309 SLE patients and 167 controls completed the baseline carotid ultrasound studies. Of those, 210 SLE patients and 100 controls returned for a followup ultrasound. Failure to complete a followup study was attributed to death (n = 5), loss of contact information (n = 14), moving

out of the area (n = 23), refusal (n = 5), scheduling difficulties (n = 70), or undergoing the baseline carotid ultrasound test after June 30, 2009 (insufficient time for followup) (n = 60). There were no significant demographic or clinical differences between these subjects and the larger baseline cohort. Detailed data on the patients who completed both the baseline and the followup ultrasound studies are presented in Table 1.

The study was approved by the Institutional Review Boards at UCLA and Cedars-Sinai Medical Center. All participants gave their written informed consent.

Sample collection

All eligible subjects provided a fasting blood sample, underwent a carotid ultrasound, and completed a set of questionnaires. Plasma levels of lipids, homocysteine, and high-sensitivity C-reactive protein (hsCRP) were measured in samples at the UCLA clinical laboratory using standard methods. On the day of plasma sampling, SLE disease activity was assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (29). Organ damage was determined using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (30). Body mass index (BMI) was calculated from height and weight measurements. Information about cardiovascular events, cardiac risk factors, and current medications was obtained at baseline and at followup from self-administered health history questionnaires and confirmed by a study physician using chart review.

Carotid ultrasound

B-mode gray-scale, color, and spectral Doppler techniques were used to investigate the carotid arteries. All ultrasounds were performed by 4 registered vascular technologists, who were trained to perform the studies according to a preset protocol (7). The same radiologist (NR) interpreted all studies, and was blinded with regard to the patients' demographic characteristics, SLE status, and any previous ultrasound results. The same ultrasound unit (Iu22; Philips Medical Systems) was used to scan all subjects.

The following anatomic sites were examined for the presence of atherosclerotic plaque, defined as the presence of focal protrusion into the arterial lumen with a thickness exceeding that of the surrounding wall of at least 50%: the bilateral common carotid, internal carotid, external carotid, and carotid bulbs. The number, location, and sonographic appearance of the plaques were recorded. IMT of the far wall of the distal common carotid artery was measured 1 cm proximal to the flow divider and at end diastole, using automated QLab software (Philips Medical Systems). IMT was never measured at the level of a plaque, and results are presented as the mean of 3 values in the left and right segments. This definition of plaque has been found to be an independent predictor of coronary heart disease events in the general population (31).

Measurement of biomarkers

Enzyme-linked immunosorbent assay kits were used to measure plasma levels of leptin (BioVendor), adiponectin, apolipoprotein A-I, and sTWEAK (R&D Systems). HDL function was measured as described previously (7,9), using a cell-free assay based on the

ability of HDL to prevent oxidation. Normal HDL prevents oxidation of LDL and dichlorofluorescein diacetate (DCF-DA), which releases a fluorochrome upon interaction with lipid oxidation products (DCF). To determine HDL function, the change in fluorescence intensity (in fluorescence units [FU]) from oxidation of DCF/LDL in the presence or absence of test HDL was measured. LDL was prepared from normal plasma as previously described (9,32), and HDL was prepared from test plasma using a dextran sulfate magnetic bead reagent (33). Twenty-five microliters of LDL cholesterol (100 μg/ml) was mixed with 6.25 μl of test HDL (100 μg HDL cholesterol/ml) in black, flat-bottomed polystyrene microtiter plates and incubated at 37°C with rotation for 30 minutes. Twenty-five microliters of 2.0 mg/ml DCF solution was then added to each well, mixed, and incubated at 37°C for 1 hour with rotation. Fluorescence was determined with a SpectraMax Gemini XS Fluorescence Microplate Reader (Molecular Devices) plate reader at an excitation wavelength of 485 nm, emission wavelength of 530 nm, and cutoff of 515 nm, with the sensitivity of the photomultiplier set at medium. Values of DCF activated by LDL in the absence of HDL were normalized to 1.0 FU as the positive control. In assays with test HDL added, FU values >1.0 indicate HDL that is dysfunctional and proinflammatory (piHDL); FU values <1.0 indicate that the HDL is antiinflammatory. Each assay was performed in a blinded manner, and the interassay and intraassay variation was <8%.

Statistical analysis

Data were analyzed using SPSS version 13.0. Skewed continuous variables were logarithmically transformed to attain a normal distribution (nontransformed data are presented herein to facilitate interpretation of the results). For variables that did not attain a normal distribution after 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 nonparametric variables, and the chi-square test or Fisher's exact test for categorical variables. The significance level was set at *P* values less than 0.05. Multiple regression was used to build models identifying risk factors associated with plaque and high IMT in SLE patients (logistic regression was used for categorical outcome variables such as plaque presence, and linear regression was used for continuous outcomes such as IMT).

Salford Predictive Modeling software was also used to identify significant predictors for the presence of carotid plaque. This software creates multiple classification trees for prediction, identifies those independent variables that best segregate as important predictors, and identifies the most predictive cutoff point for each independent variable (34). All demographic variables, traditional cardiac risk factors, markers of SLE disease activity and damage, and biomarkers were entered into the software; the variables/cutoff points that were identified as most predictive for plaque were then evaluated with univariate and multivariate regression analyses.

RESULTS

Association of traditional cardiac risk factors and demographic variables with carotid artery plaque on baseline or followup ultrasound

Subjects underwent followup carotid ultrasound at a mean ± SD of 29.6 ± 9.7 months after the baseline ultrasound (range 18–64 months). In total, 29% of SLE patients and 28% of control subjects demonstrated ≤1 carotid plaque on the baseline or followup ultrasound. At the followup ultrasound, 22% of SLE patients and 16% of control subjects had plaque progression (new plaque), while 7.1% of SLE patients and 12% of control subjects had stable plaque. One SLE patient (0.5%) and 5% of control subjects had plaque regression (*P* not significant for all comparisons). The mean time from the baseline to the followup carotid ultrasound was not different between the subjects with and those without plaque progression.

Univariate analysis was used to determine whether any baseline traditional cardiac risk factors, SLE disease factors, or demographic variables were predictive of the presence of carotid plaque at baseline and/or followup (Tables 1 and 2). The following variables were significantly associated with carotid plaque in both the SLE group and the control group: older age, increased total cholesterol level, increased LDL cholesterol level, and any dyslipidemia. In SLE patients, additional factors were significant, including higher BMI, family history of cardiovascular disease, history of diabetes, African American race, baseline homocysteine level ≥12 μmoles/liter, and longer disease duration. Increased hsCRP and triglyceride levels were associated with carotid plaque in control subjects only (Table 2). Treatment with statins was initiated during the study period in 10% of SLE patients and 6% of controls; statin initiation was significantly associated with carotid plaque in controls but not in SLE patients (Table 1).

Association of carotid plaque with nonstandard biomarkers

Univariate analysis was used to determine whether any inflammatory biomarkers were associated with the presence of plaque detected on the baseline or followup ultrasound. Higher quantity and extent of piHDL function, increased plasma leptin levels, and increased plasma sTWEAK levels were significantly associated with the presence of carotid plaque (Table 2).

Using Salford Predictive Modeling software, the most significant independent predictors and cutoff points were as follows: piHDL function ≥0.94 FU, leptin levels ≥34 ng/ml, sTWEAK levels ≥373 pg/ml, homocysteine levels ≥12 μmoles/liter, age ≥48 years, and history of diabetes. These variables were designated the Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE, or PREDICTS.

Logistic regression analysis determined which variables were most consistently associated with any carotid plaque at baseline or followup in SLE patients. The model included individual PREDICTS variables, other significant predictors on univariate analysis, and traditional cardiac and SLE-associated factors that are known potential confounders for our biomarkers of interest (e.g, hypertension, BMI, tobacco use, and statin use). Independent

predictors of carotid plaque included age ≥48 years, history of diabetes, high piHDL function, increased plasma leptin levels, and increased plasma sTWEAK levels (Table 3).

Better predictive capacity of a high-risk PREDICTS score for ATH in SLE patients, when compared with individual biomarkers or traditional cardiac risk factors

The overall profile for the prediction of any longitudinal carotid plaque was evaluated for each cardiac risk factor and biomarker by calculating the positive predictive value (PPV) and negative predictive value (NPV), the specificity, and the sensitivity (Table 4). For example, history of diabetes had a specificity of 98% for the presence of plaque; however, the sensitivity was only 13%. A combination of ≥3 traditional cardiac risk factors also had good specificity but low sensitivity. High piHDL function and increased sTWEAK levels individually had high NPV but low PPV.

When the PREDICTS markers were grouped together to classify a high-risk profile, defined as ≥3 positive biomarkers or ≥1 biomarker plus a history of diabetes, it had the best overall predictive profile of any of the variables tested (Table 4). The high-risk PREDICTS profile also had the best overall predictive profile for incident plaque, with a sensitivity of 81%, specificity of 79.2%, PPV of 40.4%, NPV of 95.4%, and area under the receiver operating characteristic curve of 0.80 (95% confidence interval [95% CI] 0.71–0.90) (results available from the corresponding author upon request).

Multivariate analysis using PREDICTS as a single variable showed that SLE patients with the high-risk PREDICTS profile had 27.7-fold increased odds ($P < 0.001$) for the presence of any plaque on the baseline or followup carotid ultrasound (Table 5). In a separate logistic regression analysis in control subjects, the high-risk PREDICTS profile conferred 8.1-fold (95% CI 1.8–36.4) increased odds for the presence of carotid plaque ($P = 0.006$). A history of hypertension was also a significant independent predictor in control subjects (OR 9.4, 95% CI 1.5–60.4, $P = 0.019$).

Association of high-risk PREDICTS profile with a higher rate of ATH progression over time

A high PREDICTS score was also associated with progression of subclinical ATH over time (Table 6). In univariate analyses, SLE patients with a high PREDICTS score were significantly more likely to have new plaque progression and a higher mean IMT at followup. They also had a higher rate of change in IMT per year and a higher mean number of new plaques per year (Table 6).

Multivariate analyses for predictors of plaque progression in SLE included the significant predictors identified on univariate analysis, potential confounders, and the baseline presence of carotid plaque. The only variable that remained significantly associated with carotid plaque progression using logistic regression was a high PREDICTS score, with an OR of 15.5 (95% CI 5.3–45.3, $P < 0.001$). The high-risk PREDICTS profile was also significantly associated with the mean change in IMT per year in SLE patients, as determined using linear regression ($P = 0.004$).

Five subjects in our cohort experienced a documented incident cardiovascular event, and 17 experienced a cerebrovascular event; all of these events occurred in patients with SLE.

Among the 5 SLE patients who had a cardiovascular event, all had a high baseline PREDICTS score ($P = 0.01$). Nine of the 17 patients with a cerebrovascular event had a high baseline PREDICTS score (*P* not significant).

DISCUSSION

We found that the PREDICTS panel of 4 inflammatory biomarkers and 2 traditional cardiac risk factors (age and diabetes), as compared with individual bio-markers or risk factors, had overall better predictive capacity for the presence, progression, or acquisition of carotid artery plaque in SLE patients who were followed up for ~2 years. The PREDICTS profile also demonstrated a better predictive capacity than a panel of traditional cardiac risk factors. Thus, PREDICTS is a good instrument for identifying SLE patients at increased risk of developing ATH in our cohort. Future studies will be needed to validate PREDICTS in other lupus cohorts.

Multiple recent studies in individuals from the general population without any history of CVD showed that the addition of nonstandard markers (including lipid-related markers and measures of inflammation, endothelial function, fibrinolysis, and oxidant stress) to risk scores containing standard cardiac risk factors led to only slight improvement in the prediction of cardiovascular events (35–38) or progression of subclinical ATH (39). It may be, however, that novel biomarkers have a greater impact on risk prediction in higher-risk populations and in populations in whom alternate pathways play a more important role in the pathogenesis of disease than traditional risk factors; thus, PREDICTS might be used to identify risk more effectively in higher-risk populations such as patients with SLE. Our finding that a panel combining inflammatory biomarkers and select traditional risk factors is more predictive of subclinical ATH than are traditional risk factors alone supports the hypothesis that inflammatory processes play a vital role in the development of ATH in SLE. PREDICTS was surprisingly also significantly predictive of subclinical ATH in our female control subjects. Although these results are intriguing, larger and longer studies are necessary to determine how accurately PREDICTS assesses cardiovascular risk in both the general population and SLE populations.

Each of the biomarkers identified in the PREDICTS profile has been linked to both SLE and CVD in the non-lupus population. These markers also appear to be direct contributors to the pathogenesis of plaque, as opposed to being mere passive bystanders associated with ATH. For example, homocysteine is thought to exert its atherogenic effects through oxidative damage (40), and homocysteine-induced oxidative stress causes endothelial dysfunction (41) and lipid peroxidation (42).

Proinflammatory HDL also contributes to endothelial dysfunction (43) and impairs reverse cholesterol transport (9). We previously demonstrated that the presence of piHDL in SLE patients results in up-regulation of monocyte chemotaxis and ATH-promoting transcripts in monocytes. Inhibition of piHDL, through reduction of piHDL oxidation or blockade of platelet-derived growth factor receptor β kinase activity, restored normal monocyte chemotaxis (33).

Similarly, elevated leptin levels induce oxidative stress in endothelial cells (14) and cardiomyocytes (13). When exogenous leptin was administered to lupus-prone mice, formation of piHDL and atherosclerotic plaque was accelerated (44), suggesting that there is biologic interplay between these 2 PREDICTS components.

To our knowledge, this is the first study to link high plasma TWEAK levels to ATH in SLE. TWEAK might be a potential biomarker for active SLE renal disease; high urinary TWEAK levels were significantly associated with lupus nephritis (45). TWEAK is expressed in the kidney and acts synergistically with oxidized LDL in promoting inflammatory gene expression in renal tubular cells (46). Administration of TWEAK to apolipoprotein E–deficient mice resulted in a significant increase in plaque, which was inhibited when mice were pretreated with anti-TWEAK antibodies (46). In contrast to these data suggesting that there is an association between sTWEAK and ATH, other clinical data have suggested that plasma sTWEAK levels are inversely related to subclinical ATH in the general population (47). However, another study showed that sTWEAK levels were significantly elevated in patients with acute myocardial infarction compared to patients with stable coronary disease and healthy controls, and higher levels were associated with adverse short-term post–myocardial infarction outcomes (48). The sTWEAK levels also positively correlated with coronary artery calcification (49) and increased mortality (24) in patients undergoing hemodialysis.

There are some limitations to our study. The median followup time for subjects in our cohort was 2.3 years; thus, the presence of subclinical ATH, rather than cardiovascular events, was the end point assessed. It is possible that the PREDICTS profile could not be used to predict future cardiovascular events over time; however, it is noteworthy that all 5 SLE patients with a cardiovascular event in our cohort had both a high PREDICTS score and carotid plaque ($P = 0.03$) at baseline. The PREDICTS panel seems to be associated more strongly with cardiovascular events than with cerebrovascular events in our cohort, but given the small number of events seen in this relatively short-term study, we interpret these data with caution.

Unlike the published findings in other cohorts (4), the incidence of subclinical ATH in our lupus cohort was not significantly higher than that in the healthy control cohort, and plaque prevalence in both the SLE group and control group at baseline was lower than has been previously reported (4,50). Individuals with active renal disease or statin use were excluded, and thus there was a selection bias that excluded patients with known inflammation and hyperlipidemia (27). The age of the SLE patients in our cohort at study entry was also slightly lower (mean ± SD 41.8 ± 13.0 years) compared to that in other cohorts (4,50). Interestingly, there was a trend toward accelerated progression of subclinical ATH in SLE patients compared to healthy controls, as new plaque progression was seen in 48% of SLE patients and 25% of controls ($P = 0.1$). The number of new plaques per year ($P = 0.053$) and change in IMT per year ($P = 0.06$) also showed a trend toward higher values in SLE patients compared to controls. It is possible that there is a critical age threshold during which the rates of ATH progression in SLE patients and controls begin to separate. It is also possible that the SLE population in Los Angeles differs significantly from that in other areas.

Finally, although we examined multiple biomarkers for ATH in SLE patients both in this study and in previous studies (7,11), our study was not exhaustive. It is likely that other additional biomarkers have been or will be identified as promising candidates. Future studies will be needed to assess the utility of adding or substituting alternate biomarkers into the PREDICTS panel.

In summary, the PREDICTS panel—a combination panel of independent variables, including 4 inflammatory biomarkers and 2 traditional cardiac risk factors—had overall better predictive capacity for the longitudinal presence of plaque in SLE patients than did any individual biomarker or traditional risk factor. A high PREDICTS score conferred 28-fold increased odds for the presence of any current, progressive, or acquired carotid plaque in SLE patients, and also was significantly associated with higher rates of plaque and IMT progression. PREDICTS could aid clinicians in identifying SLE patients at risk of ATH. Future studies will be needed to determine whether PREDICTS can be used to predict cardiovascular events in SLE patients and controls from other centers, and whether identification of high-risk subjects can direct future preventative treatment strategies.

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Table 1

Baseline demographic and clinical characteristics of the patients with systemic lupus erythematosus (SLE) and healthy controls without plaque or with a history of any plaque at baseline or followup*

	Control subjects			SLE patients		
Baseline characteristic	**No plaque (n = 72)**	**Any plaque (n = 28)**	***P*†**	**No plaque (n = 149)**	**Any plaque (n = 61)**	***P*†**
Time to second ultrasound, mean ± SD months	28.0 ± 10.0	29.2 ± 9.7	NS	30.6 ± 9.8	29.5 ± 8.6	NS
Age, mean ± SD years	40.5 ± 11.8	54.6 ± 10.1	<0.001	39.6 ± 13.5	51.9 ± 10.2	<0.001
History of CAD	0	0	–	0	2 (3.2)	NS
History of CVE	0	0	NS	9 (6.0)	4 (6.6)	NS
Body mass index, mean ± SD kg/m^2	23.7 ± 5.1	25.3 ± 5.8	NS	25.7 ± 5.9	28.0 ± 7.1	0.03
Family history of CVD	10 (13.9)	7 (25)	NS	31 (20.8)	23 (37.7)	0.01
History of hypertension	6 (8.3)	10 (35.7)	0.001	41 (27.5)	25 (41)	0.06
History of dyslipidemia	13 (18.1)	13 (46.4)	0.004	22 (14.8)	20 (32.7)	0.003
History of diabetes	0	1 (3.6)	NS	3 (2.0)	8 (13.1)	0.003
Smoking history						
Ever smoker	20 (27.8)	8 (28.5)	NS	44 (29.5)	18 (29.5)	NS
Current smoker	8 (11.1)	3 (10.7)	NS	10 (6.7)	5 (8.1)	NS
Ethnicity/race						
White	40 (55.6)	17 (60.7)	NS	79 (53)	25 (41.0)	NS
Asian or Pacific Islander	16 (22.2)	4 (14.3)	NS	24 (16.1)	9 (14.8)	NS
African American	4 (5.5)	3 (10.7)	NS	8 (5.4)	12 (19.7)	0.001
Hispanic	9 (12.5)	3 (10.7)	NS	32 (21.5)	9 (14.0)	NS
Mixed or other	3 (4.2)	1 (3.6)	NS	6 (4.0)	6 (9.8)	NS
Statins initiated	1 (1.4)	5 (17.8)	0.007	13 (8.7)	8 (13.1)	NS
Disease duration, mean ± SD years	NA	NA	NA	11.4 ± 8.0	14.9 ± 11.4	0.01
SELENA–SLEDAI, mean ± SD	NA	NA	NA	3.5 ± 4.0	3.9 ± 3.5	NS
SDI score, mean ± SD	NA	NA	NA	1.2 ± 1.5	1.4 ± 2.0	NS
Any aCL antibodies	NA	NA	NA	59 (39.6)	17 (27.8)	NS
History of glomerulonephritis	NA	NA	NA	44 (29.7)	14 (23.0)	NS
Baseline medication						
Mycophenolate mofetil	NA	NA	NA	12 (19.7)	44 (23.3)	NS

Baseline characteristic	Control subjects			SLE patients		
	No plaque (n = 72)	Any plaque (n = 28)	P†	No plaque (n = 149)	Any plaque (n = 61)	P†
Hydroxychloroquine	NA	NA	NA	36 (59.0)	124 (65.6)	NS
Azathioprine	NA	NA	NA	4 (6.6)	26 (13.8)	NS
Prednisone						
Current dose, mean ± SD mg	NA	NA	NA	4.8 ± 9.1	4.3 ± 7.7	NS
6-month dose, mean ± SD mg	NA	NA	NA	687.0 ± 1,041.1	821.7 ± 1,304.8	NS
Lifetime use >20 gm	NA	NA	NA	44 (29.5)	18 (29.5)	NS

* History of coronary artery disease (CAD) was defined as either a history of myocardial infarction (MI) or documented CAD on angiogram or stress test. History of cerebrovascular events (CVE) included transient ischemic attacks (confirmed by a physician) and stroke (confirmed by appropriate imaging). Family history of coronary vascular disease (CVD) was defined as any parental history of MI before age 60 years. Dyslipidemia was defined as any of the following, either alone or in combination: levels of low-density lipoprotein cholesterol ≥130 mg/dl, total cholesterol ≥200 mg/dl, high-density lipoprotein cholesterol ≥40 mg/dl, and/or triglycerides ≥150 mg/dl. Hypertension was defined as use of antihypertensive medication or systolic blood pressure >140 mg Hg or diastolic blood pressure >90 mm Hg. Diabetes mellitus was defined as a fasting glucose level ≥7.0 mmoles/liter (126 mg/dl) or treatment with insulin or an oral hypoglycemic agent. Smokers were designated as subjects who had smoked any cigarettes within the prior 3 months. Race/ethnicity categorization was based on patient self-description. Except where indicated otherwise, values are the number (%) of subjects. NS = not significant; NA = not applicable; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; aCL = anticardiolipin.

† Only *P* values <0.1 are shown.

Table 2

Baseline lipid and inflammatory biomarker measurements in patients with systemic lupus erythematosus (SLE) and healthy controls without plaque or with a history of any plaque at baseline or followup*

	Control subjects			SLE patients		
Baseline measurement	**No plaque (n = 72)**	**Any plaque (n = 28)**	***P*†**	**No plaque (n = 149)**	**Any plaque (n = 61)**	***P*†**
Total cholesterol, mg/dl	188.9 ± 39.5	208.3 ± 41.6	0.03	185.0 ± 41.8	199.1 ± 41.0	0.03
HDL, mg/dl	60.8 ± 15.2	60.7 ± 15.3	NS	57.3 ± 17.9	58.3 ± 17.1	NS
LDL, mg/dl	107.5 ± 32.8	120.0 ± 30.9	0.09	105.7 ± 33.8	116.5 ± 35.8	0.04
Triglycerides, mg/dl	104.0 ± 50.4	139.5 ± 81.2	0.01	111.7 ± 75.7	112.8 ± 45.7	NS
High-sensitivity CRP, mg/liter	1.6 ± 1.7	4.0 ± 6.7	0.05	3.2 ± 7.9	3.0 ± 5.1	NS
Adiponectin, μg/ml	13.3 ± 6.3	13.8 ± 8.0	NS	14.3 ± 7.6	16.3 ± 10.2	NS
Apolipoprotein A–I, mg/ml	0.9 ± 1.0	1.7 ± 3.3	NS	1.2 ± 1.5	1.6 ± 3.03	NS
Homocysteine ≥12 mmoles/liter, no. (%)	9 (12.5)	8 (28.6)	0.057	41/146 (28.1)	26 (42.6)	0.04
Leptin						
Plasma level, ng/ml	10.3 ± 8.5	24.5 ± 22.3	<0.001	20.9 ± 23.9	32.1 ± 28.8	0.005
Plasma level ≥34 ng/ml, no. (%)	1 (1.4)	8 (28.6)	<0.001	14 (9.4)	22 (36.1)	<0.001
piHDL function						
Level, FU	0.67 ± 0.3	1.0 ± 0.66	0.003	0.98 ± 0.56	1.30 ± 1.1	<0.001
Function ≥0.94 FU, no. (%)	12 (16.7)	15 (53.6)	<0.001	59 (39.6)	50 (82.0)	<0.001
Soluble TWEAK						
Plasma level, pg/ml	207.94 ± 395.58	634.98 ± 1,545.96	NS	229.94 ± 846.31	523.69 ± 898.94	0.002
Plasma level ≥373 pg/ml, no. (%)	61 (84.7)	25 (89.3)	NS	120 (80.5)	60 (98.4)	<0.001

* Except where indicated otherwise, values are the mean ± SD. HDL = high-density lipoprotein; NS = not significant; LDL = low-density lipoprotein; CRP = C-reactive protein; piHDL = proinflammatory HDL; FU = fluorescence units.

† *P* values in univariate analysis were determined using Student's *t*-test, Mann-Whitney test, or chi-square test. Only *P* values <0.1 are shown.

Table 3

Associations of traditional cardiac risk factors and nonstandard biomarkers with the presence of any carotid plaque on baseline or longitudinal ultrasound in patients with systemic lupus erythematosus*

Explanatory variable	Odds ratio	95% CI	*P*
Age ≥48 years (yes, no)	4.1	1.7–10.3	0.002
History of dyslipidemia	2.6	0.8–8.2	NS
History of diabetes (yes, no)	61.8	6.4–598.1	<0.001
Hypertension (yes, no)	0.9	0.35–2.4	NS
History of tobacco use (yes, no)	0.6	0.2–1.5	NS
Family history of cardiovascular disease (yes, no)	2.0	0.7–5.2	NS
Body mass index (in kg/m^2)	0.997	0.92–1.07	NS
African American race (yes, no)	3.5	0.8–15.7	0.1
Lifetime prednisone use >20 gm	0.5	0.28–1.6	NS
Initiation of statin therapy	1.9	0.4–9.2	NS
piHDL ≥0.94 FU	9.1	3.3–24.6	<0.001
Leptin ≥34 ng/ml	7.3	2.2–24.0	0.001
Soluble TWEAK ≥373.0 pg/ml	28.8	2.9–281.1	0.004
Homocysteine ≥12 μmoles/liter	1.2	0.5–2.9	NS

*Associations were assessed by logistic regression. 95% CI = 95% confidence interval; NS = not significant; piHDL = proinflammatory high-density lipoprotein; FU = fluorescence units.

Table 4

Prediction profiles for individual biomarkers and traditional risk factor or biomarker panels in analyses of association with any carotid plaque on longitudinal ultrasound in patients with systemic lupus erythematosus (SLE)*

Characteristic	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	AUC (95% CI)
History of diabetes	13.1	98.0	72.7	73.3	0.56 (0.47–0.65)
piHDL ≥0.94 FU	82.0	61.0	45.5	89.0	0.71 (0.64–0.79)
Leptin ≥34 ng/ml	36.1	90.6	61.1	77.6	0.63 (0.54–0.72)
Soluble TWEAK ≥373 pg/ml	72.1	48.9	36.7	81.1	0.59 (0.51–0.69)
Homocysteine ≥12 μmoles/liter	42.6	71.9	50	85.5	0.60 (0.51–0.69)
Traditional cardiac risk factors					
≥3 risk factors†	24.6	91.3	53.6	74.7	0.58 (0.49–0.67)
PREDICTS factors‡					
≥1 risk factor	100	6.7	30.5	100	0.53 (0.45–0.62)
≥2 risk factors	90.2	36.9	36.9	90.2	0.64 (0.56–0.71)
≥4 risk factors	50.8	94	77.5	82.4	0.72 (0.64–0.81)
≥3 risk factors or history of diabetes + ≥1 risk factor in SLE patients	88.5	79.2	63.5	94.4	0.84 (0.78–0.90)
≥3 risk factors or history of diabetes + ≥1 risk factor in healthy controls	57.1	88.8	66.6	84.2	0.73 (0.61–0.85)

* AUC = area under the receiver operating characteristic curve; 95% CI = 95% confidence interval.

† The traditional cardiac risk factor panel includes age ≥48 years, any history of diabetes, hypertension, dyslipidemia, or tobacco use.

‡ The Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with Systemic Lupus Erythematosus (PREDICTS) panel includes age ≥48 years, proinflammatory high-density lipoprotein (piHDL) ≥0.94 fluorescence units (FU), leptin levels ≥34 ng/ml, soluble TWEAK levels ≥373 pg/ml, and homocysteine levels ≥12 μmoles/liter.

Table 5

Associations of the PREDICTS variables with the presence of any carotid plaque on baseline or longitudinal ultrasound in patients with systemic lupus erythematosus*

Explanatory variable	Odds ratio	95% CI	*P*
History of dyslipidemia (yes, no)	3.2	1.06–9.8	0.04
Hypertension (yes, no)	0.8	0.3–2.0	NS
Current tobacco use (yes, no)	1.6	0.3–7.5	NS
Family history of cardiovascular disease (yes, no)	1.3	0.5–3.2	NS
Body mass index (in kg/m^2)	1.01	0.95–1.07	NS
African American race (yes, no)	4.6	1.1–18.6	0.03
Lifetime prednisone use >20 gm (yes, no)	0.6	0.2–1.7	NS
Initiation of statin therapy (yes, no)	0.7	0.2–2.5	NS
Disease duration	1.03	0.98–1.09	NS
High PREDICTS score (yes, no)†	27.7	10.6–72.7	<0.001

* Associations were determined by logistic regression. 95% CI = 95% confidence interval; NS = not significant.

† Variables include age ≥48 years, proinflammatory high-density lipoprotein levels ≥0.94 fluorescence units, leptin levels ≥34 ng/ml, soluble TWEAK levels ≥373 pg/ml, and homocysteine levels ≥12 μmoles/liter. A high Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with Systemic Lupus Erythematosus (PREDICTS) score was defined as the presence of ≥3 of the risk factors or history of diabetes plus ≥1 of the risk factors.

Table 6

Associations of the PREDICTS variables with cardiovascular events, plaque, and progression of intima-media thickness (IMT) in patients with systemic lupus erythematosus (SLE) and healthy controls*

	Control subjects			SLE patients		
Explanatory variable	**Low PREDICTS score (n = 76)**	**High PREDICTS score (n = 24)**	***P***	**Low PREDICTS score (n = 125)**	**High PREDICTS score (n = 85)**	***P***
Any new CAD at followup	0	0	–	0	5 (5.9)	0.01
Any new CVE at followup	0	0	–	8 (6.4)	9 (10.5)	NS
Any carotid plaque, baseline or followup	12 (15.8)	16 (66.7)	<0.001	7 (5.6)	54 (63.5)	<0.001
Any new plaque progression	10 (13.2)	6 (25.0)	NS	5 (4.0)	41 (48.2)	<0.001
No. of new plaques/year, mean ± SD	0.09 ± 0.29	0.03 ± 0.51	NS	0.03 ± 0.14	0.36 ± 0.52	<0.001
IMT at followup, mean ± SD mm	0.56 ± 0.12	0.63 ± 0.11	0.014	0.52 ± 0.09	0.67 ± 0.16	<0.001
ΔIMT/year, mean ± SD mm	0.01 ± 0.04	0.02 ± 0.04	NS	0.01 ± 0.03	0.03 ± 0.04	<0.001

* Except where indicated otherwise, values are the number (%) of subjects. PREDICTS = Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE; CAD = coronary artery disease (defined as myocardial infarction or angina confirmed with angiogram or stress test); CVE = cerebrovascular event (defined as transient ischemic attacks confirmed by a physician or stroke confirmed by appropriate imaging); NS = not significant.