

Resistin Levels in Lupus and Associations with Disease-specific Measures, Insulin Resistance, and Coronary Calcification

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ABSTRACT. Objective. To evaluate levels of resistin in female subjects with systemic lupus erythematosus (SLE) compared to age and race-matched controls and to determine the relationship between resistin and systemic inflammation, disease measures, and coronary artery calcification (CAC).

Methods. Resistin levels were measured on stored samples from 159 women with SLE and 70 controls as an extension of a previous cross-sectional study. Spearman correlations and multivariable regressions were used to examine whether resistin levels were associated with SLE, disease-specific and inflammatory markers, insulin resistance, and CAC.

Results. In a multivariable linear regression model, a diagnosis of SLE was significantly associated with higher resistin levels independent of age, race, renal function, body mass index (BMI), high-sensitivity CRP (hsCRP), hypertension, diabetes, and steroid use. In SLE, resistin levels correlated positively with Systemic Lupus International Collaborating Clinics Damage Index, glomerular filtration rate (GFR), hsCRP, erythrocyte sedimentation rate, homocysteine, and disease duration (all $p < 0.03$). Resistin level did not correlate with markers of insulin resistance or body adiposity, including homeostatic model assessment or BMI. Resistin levels were significantly elevated in SLE cases with CAC compared to cases without CAC (16.58 vs 13.10 ng/ml, respectively; $p = 0.04$). In multivariate logistic regression, the association was not present after adjustment for age, race, and GFR.

Conclusion. SLE was independently associated with higher resistin levels. Among subjects with SLE, higher resistin level correlated positively with renal dysfunction, inflammatory markers, and disease damage but not with insulin resistance or BMI. SLE cases with CAC had higher resistin levels than cases without CAC; however, this relationship was dependent on other established risk factors. (J Rheumatol First Release Sep 1 2011; doi:10.3899/jrheum.110237)

Key Indexing Terms:

RESISTIN
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SYSTEMIC LUPUS ERYTHEMATOSUS
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Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that occurs predominantly in women¹. Individuals with SLE have a greater risk of developing pre-

mature atherosclerotic cardiovascular disease (ASCVD) than the general population^{2,3}. Factors traditionally associated with ASCVD, such as hypertension (HTN), diabetes, and renal disease, are increased in patients with SLE. However, SLE is a risk factor for ASCVD independent of known risk factors⁴. We have shown that hyperhomocysteinemia and disease duration are associated with the presence of coronary artery calcification (CAC) in patients with SLE, as determined by electron beam computed tomography (EBCT)⁵. Additional biomarkers to identify premature ASCVD in SLE are under investigation.

Obesity has been linked to ASCVD in the general population. One of the most profound changes in our understanding of the metabolic consequences of obesity has been the recognition that obesity is an inflammatory disease state^{6,7}. Central body adiposity and specifically insulin resistance are associated with increased systemic levels of inflammatory markers such as tumor necrosis factor- α , interleukin 6, and C-reactive peptide as well as monocyte chemoattractant protein (MCP-1)^{8,9,10,11}. It is thought that

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this inflammation may be the common mediator linking the pathogenesis of obesity, diabetes, and atherosclerosis. It is possible that this observed pattern in patients with abdominal obesity may have particular relevance in patients with inflammatory diseases such as SLE. Recent data do suggest that SLE is associated with an insulin-resistant state^{12,13,14}.

Adipokines, factors released from adipocytes, stimulate inflammatory activity that may be involved in the etiology of insulin resistance. A recently identified adipokine, resistin, has been found to be elevated in obese and insulin-resistant rodents and humans¹⁵. In rodents, resistin is made exclusively by adipocytes, while in humans, resistin is made primarily in macrophages¹⁶. In humans, resistin is also induced by acute inflammatory stimuli¹⁷ and has proinflammatory properties. *In vitro* studies suggest that homocysteine (Hcy), elevated in inflammatory states, may impair the insulin-signaling pathway and induce an increase in resistin expression¹⁸. Resistin has also been shown to be elevated in SLE, and to correlate with markers of inflammation, glomerular filtration rate (GFR), and steroid use¹⁹. Alterations in resistin have also been found in other autoimmune diseases, such as Sjögren's syndrome and ankylosing spondylitis^{20,21}. In contrast, other studies show no difference in resistin levels among subjects with SLE compared to controls^{22,23,24}.

In the general population, resistin has been associated with atherosclerosis. Reilly, *et al*²⁵ showed that resistin was associated with CAC among 879 asymptomatic subjects from the Study of Inherited Risk of Coronary Atherosclerosis, independent of traditional risk factors including the metabolic syndrome and high sensitivity C-reactive protein (hsCRP). In a number of other at-risk populations, resistin levels have been found to be predictive of coronary atherosclerosis, coronary events, and mortality. Among diabetic subjects, resistin levels were higher among those with ischemic stroke²⁶. In subjects experiencing a recent myocardial infarction, or undergoing percutaneous coronary interventions, resistin levels correlated with severity of coronary atherosclerosis and predicted further events^{27,28,29}.

We evaluated resistin levels and measures of insulin resistance in a previously described⁵ case cohort study of women with SLE and age-matched and race-matched controls in order to determine whether resistin levels are elevated in SLE, and which factors are associated with elevated resistin levels among SLE subjects. We also evaluated their possible association with other known risk factors for ASCVD and with the presence of CAC on EBCT.

MATERIALS AND METHODS

Study subjects. Consecutive nonpregnant women patients with SLE over the age of 18 years (n = 159) and nonpregnant female controls matched for age (± 2 yrs) and race without autoimmune disease (n = 132) were recruited from the University of Pennsylvania clinics and invited to participate in a previous study. Full characteristics of the SLE cohort and controls and results from that study have been published⁵. Patients with SLE were required to fulfill at least 4 of the American College of Rheumatology revised criteria for the classification of SLE^{30,31}. That study was approved by the Institutional

Review Board of the University of Pennsylvania, and written informed consent was obtained from each participant. In our substudy, stored serum was sent for measurement of resistin levels for all patients with SLE (n = 159) and a randomly selected portion of controls (n = 70).

Clinical assessments. Medical history and physical examination data were collected for all subjects at their single study visit. Body mass index (BMI) was calculated using the standard method. All participants had a physical examination, electrocardiography, and EBCT, and a fasting blood sample was drawn, as described⁵. Clinical characteristics have been reported^{5,32}.

We used a modified version of the International Diabetes Federation definition of the metabolic syndrome³³. Waist circumference measurement was not available, thus metabolic syndrome was considered present in an obese patient (BMI > 30) with any 2 of the following: (1) elevated triglyceride level > 150 mg/dl; (2) high-density lipoprotein (HDL) level < 40 mg/dl in men and < 50 mg/dl in women; (3) fasting glucose > 100 mg/dl [or previous diagnosis of diabetes (DM)]; or (4) a previous diagnosis of HTN.

Laboratory assessments. Fasting blood samples were collected from subjects at their single study visit and frozen at -80°C until the time of evaluation. Laboratory assessments included the following: glucose, HDL, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), total cholesterol, triglycerides, fibrinogen, creatinine, Westergren erythrocyte sedimentation rate (ESR), hsCRP, MCP-1, anti-double-stranded DNA (dsDNA), and complement C3 and C4. GFR was estimated for each subject using the Modification of Diet in Renal Disease equation³⁴. Total plasma Hcy concentrations were determined using the AxSYM Homocysteine via Fluorescence Polarization Immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Insulin levels were determined using a human insulin-specific radioimmunoassay (Linco Research, St. Charles, MO, USA). Insulin resistance was estimated using the homeostatic model assessment (HOMA), calculated using the formula (fasting insulin \times fasting glucose)/22.5. Resistin concentrations in stored plasma were assessed with a commercial ELISA (Linco Research). The within-assay variation for this is 3.8%–7.0% and the between-assay variation is 7.1%–7.7%.

Electron beam computed tomography. CAC appears in the very early stages of ASCVD and progresses with the disease; CAC scores determined by EBCT reflect total atherosclerotic burden and are predictive of future cardiac events³⁵.

Patients with SLE and controls had electrocardiographic triggered scans in a GE Imatron C150 electron beam CT scanner (General Electric Medical Systems, South San Francisco, CA, USA) for 2 image acquisitions. Serial, contiguous, transverse images 3 mm thick were obtained, commencing at the root of the aorta cephalad to the coronary sinuses and proceeding caudally through the entire coronary tree (Aquarius software; Tera-Recon, San Mateo, CA, USA) as described⁵. Data were scored quantitatively in a blinded manner by a registered radiology technologist. Scores were calculated using the method described by Agatston, *et al*³⁶. Total CAC was quantified by summing across the 4 major epicardial arteries, resulting in a raw CAC score. These scores were compared with raw CAC scores from a previously established population of age-matched and sex-matched individuals whose data were preprogrammed as the control standard.

Statistical analysis. Data were analyzed on Stata 11 software. A 2-tailed p value < 0.05 was the criterion for statistical significance. Histograms, boxplots, and scatterplots were used to examine distributions, guide data transformations as needed, and assess bivariate relations. T tests and rank-sum tests (for skewed data) were performed to evaluate for differences in patient characteristics between those subjects with resistin levels above and below the median value (10 ng/ml). Since a normal range for resistin has not been determined, we used the median value to define high/low resistin. Previous studies have used similar values³⁷. Spearman correlations were performed to determine factors significantly associated with resistin levels in the SLE and control groups. Variables significantly correlated with resistin levels were used to inform regression models.

Multivariable linear regression analysis was performed to determine the association between SLE and resistin levels, adjusting for factors that have been associated with resistin levels or were associated with resistin in univariable analysis (GFR, BMI, DM, HTN, hsCRP, Hcy, steroid use, and

metabolic syndrome) to determine if these variables explained differences in resistin between SLE subjects and controls. Where resistin levels were the outcome in a linear regression model, the variable was natural-log transformed in order to fit a normal distribution. Adjusted mean values were subsequently determined using the multivariable model. To determine if associations between resistin and Hcy, GFR, and BMI were significantly different between SLE subjects and controls, we evaluated for interaction between the diagnosis of SLE and these variables.

Univariable and multivariable logistic regression analyses were performed to evaluate the association between resistin levels and the probability of an abnormal calcium score adjusting for traditional risk factors for coronary atherosclerosis. Because CAC scores were highly skewed, coronary calcium scores were converted to a binary variable (presence or absence of CAC). Resistin was evaluated as a continuous and dichotomous variable. Predetermined traditional risk factors for CAC were evaluated as potential confounders including age, race, GFR, DM, HTN, and smoking. Separately, we also evaluated Hcy and disease duration (risk factors previously associated with CAC in our cohort).

RESULTS

Sample characteristics. A full description of the demographic, clinical, and biochemical data for the original study sample has been reported⁵. Briefly, subjects with SLE and controls differed significantly in Hcy, MCP-1, CAC, VLDL, LDL, HDL, triglycerides, and hsCRP concentrations. There was also a trend toward lower GFR in SLE subjects relative to controls (87.6 vs 93.6 ml/min; $p = 0.07$). Significantly more SLE subjects than controls were treated with prednisone, beta-blockers, and antidepressants, in addition to immunosuppressive therapies (data not shown). Treatments with statins and aspirin did not differ significantly between SLE subjects and controls. This sample population represented a significantly higher percentage of self-reported diabetics in the SLE group than the control group (10.3% vs 3.0%, respectively; $p = 0.025$), although the BMI of the 2 groups was found to be similar (28.48 vs 28.89 kg/m²; $p = 0.60$). Between patients and controls, there was no significant difference in HOMA scores, insulin levels, fasting glucose levels, or in the proportion with the metabolic syndrome (all $p > 0.3$). The demographic and main clinical characteristics of patients and controls by resistin level (above or below the median value) are summarized in Table 1.

Resistin levels and diagnosis of SLE. Significant differences in mean resistin levels were observed between the SLE subjects (14.18 ± 10.94 ng/ml) and controls (9.95 ± 6.48 ng/ml; $p = 0.003$). A diagnosis of SLE was significantly associated with higher log-transformed resistin levels in a linear regression model that included age, race, BMI, GFR, hsCRP, HTN, and diabetes [$\beta = 0.19$ (0.0084, 0.37); $p = 0.040$]. The adjusted mean resistin level among SLE subjects was 12.0 ng/ml and among controls 9.3 ng/ml. When steroid use (past, present, or never) was included in the model, this association was similar [$\beta = 0.19$ (0.0054, 0.37); $p = 0.044$]. Separately, controlling for the presence of the metabolic syndrome and Hcy levels did not significantly attenuate the association. Further, adjustment for the use of statins, aspirin, and angiotensin-converting enzyme (ACE) inhibitors also did not attenuate the association (data not shown).

Resistin and factors associated with SLE. Patients with SLE who had elevated resistin levels (> 10 ng/ml) had lower BMI, lower GFR, lower albumin, and higher Hcy and hsCRP levels. In contrast, among controls, subjects with a resistin level > 10 ng/ml were younger and tended to have a higher GFR ($p = 0.08$) and lower Hcy ($p = 0.06$) level. Factors traditionally associated with disease in patients with SLE were also found to be associated with increased resistin levels in SLE cases. Hcy, proteinuria, history of renal disease, GFR, disease duration, hsCRP, and the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) were all found to have a significant correlation with resistin levels (Table 2). However, the SLE Disease Activity Index (SLEDAI) was found not to be significantly associated with resistin levels in patients with SLE. When the associated variables from Table 2 were included in a predictive multivariable linear regression model, independent predictors of a log-transformed resistin level in SLE subjects included GFR, ESR, and Hcy in a model that also included age, race, BMI, DM, and HTN.

The associations between resistin and GFR, Hcy, and BMI appeared qualitatively different (Table 2). Therefore, we tested for interaction to determine if the associations between these variables and resistin were statistically different between SLE subjects and controls in a model that included age, race, GFR, Hcy, BMI, hsCRP, DM, and HTN. A diagnosis of SLE significantly modified the association between GFR and resistin ($p = 0.05$), and the association between Hcy and resistin ($p = 0.02$). There was no significant interaction between BMI and the diagnosis of SLE on levels of resistin.

Resistin and factors associated with metabolic disease. Factors that are associated with insulin resistance, such as BMI, HOMA score, fasting glucose, insulin level, and a diagnosis of diabetes, were found to have no correlation with resistin levels among patients with SLE (Table 2). Some variables associated with the metabolic syndrome, such as triglycerides, HDL, and uric acid, were significantly correlated with resistin levels. However, the metabolic syndrome occurred with similar frequency among subjects with high and low resistin levels. Among controls, resistin levels were not significantly higher among those with metabolic syndrome compared to those without metabolic syndrome (13.0 ± 11.5 vs 9.5 ± 5.6 ng/ml; $p = 0.15$). Similarly, lupus subjects with metabolic syndrome did not have significantly higher resistin levels than those without metabolic syndrome (14.1 ± 11.5 vs 12.2 ± 9.1 ng/ml; $p = 0.31$).

Resistin and CAC. Subjects with SLE who had CAC as determined by EBCT had significantly higher resistin concentrations than SLE subjects that did not have CAC (16.58 vs 13.10 ng/ml, respectively; $p = 0.032$; Figure 1). However, as shown in Table 2, there was no significant Spearman correlation between calcium score and resistin (Spearman's rho = 0.11; $p = 0.2$). The controls who had CAC did not have

Table 1. Baseline characteristics of subjects with SLE and controls by resistin level (above or below the median value). Values are mean (SD) or median (interquartile range) if skewed.

Variable	All Participants	Resistin > 10 ng/ml	Resistin ≤ 10 ng/ml	p
SLE				
N	159	85	74	—
Age, yrs	43.2 (11.1)	43.6 (11.2)	42.6 (11.1)	0.7
White, %	38.8	38.5	39.2	0.3
Black, %	50.9	53.9	47.3	0.3
BMI, kg/m ²	28.4 (6.9)	27.4 (6.5)	29.6 (7.3)	0.05
GFR, ml/min/1.75 m ²	90.1 (32.3)	83.2 (35.8)	98.6 (25.3)	0.002
Homocysteine, μmol/l	11.6 (4.5)	12.8 (5.0)	10.2 (3.3)	< 0.001
ESR, mm/h	30.3 (25.7)	32.2 (26.3)	28.0 (25.0)	0.3
hsCRP, mg/dl	3.0 (1.0, 8.1)	3.9 (1.2, 10.2)	2.3 (0.9, 4.9)	0.02
Albumin, g/dl	3.9 (0.47)	3.8 (0.52)	4.1 (0.39)	0.007
Active smokers, %	20.7	21.1	20.3	0.9
Diabetes, %	10.3	11.0	9.5	0.8
HOMA score	3.0 (1.8, 4.2)	2.8 (1.8, 4.1)	3.2 (1.7, 4.3)	0.8
Insulin level, μU/ml	14.9 (9.6, 21.1)	13.3 (9.2, 19.2)	16.1 (10.8, 23.0)	0.2
Fasting glucose, mg/dl	83.1 (31.3)	86.0 (36.6)	79.9 (24.3)	0.3
Metabolic syndrome, %	13.7	11.8	15.7	0.5
SLICC-DI	2 (1, 3)	2 (1, 4)	1 (0, 2)	0.009
SLEDAI	4 (2, 6)	4 (2, 7)	4 (0, 6)	0.2
Disease duration, yrs	8 (3.8, 17)	10 (5, 18)	6 (3, 13)	0.005
History of nephritis, %	15.2	20.0	9.5	0.06
History of proteinuria, %	14.3	26.1	12.8	0.01
Controls				
N	70	43	27	—
Age, yrs	44.8 (9.8)	41.6 (9.0)	46.8 (9.9)	0.03
White, %	52.9	63.0	46.5	0.1
Black, %	45.7	33.3	53.5	0.1
BMI, kg/m ²	29.0 (6.4)	30.0 (6.6)	28.3 (6.3)	0.3
GFR, ml/min/1.75 m ²	93.3 (19.5)	98.3 (19.4)	90.1 (19.0)	0.08
Homocysteine, μmol/l	10.5 (2.6)	9.7 (2.6)	10.9 (2.5)	0.06
hsCRP, mg/dl	1.5 (0.6, 5.0)	1.9 (0.9, 6.9)	1.1 (0.5, 4.7)	0.1
Albumin, g/dl	4.2 (0.46)	4.1 (0.32)	4.2 (0.53)	0.6
Active smokers, %	15.8	22.2	11.6	0.2
Diabetes, %	3.75	3.7	7.0	0.6
HOMA score	2.8 (1.9, 3.8)	2.8 (1.9, 3.6)	2.9 (1.9, 3.9)	0.8
Insulin level, μU/ml	15.4 (11.8, 20.1)	15.4 (12.8, 20.3)	15.3 (11.1, 19.6)	0.6
Fasting glucose, mg/dl	85.3 (31.5)	78.7 (9.4)	89.3 (39.2)	0.3
Metabolic syndrome, %	11.4	11.1	11.6	0.9

SLE: systemic lupus erythematosus; BMI: body mass index; ESR: erythrocyte sedimentation rate; GFR: glomerular filtration rate; hsCRP: high sensitivity C-reactive protein; HOMA: homeostatic model assessment; SLICC-DI: Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI: SLE Disease Activity Index.

significantly higher resistin concentrations compared with controls who did not have CAC (11.80 vs 9.56 ng/ml; $p = 0.14$). The association between resistin levels and abnormal CAC score was confounded by age and GFR. Table 3 demonstrates the multivariable-adjusted risk of abnormal CAC by level of resistin in SLE subjects and controls. Resistin was not associated with the presence of CAC in either group after adjustment for traditional risk factors including age, race, BMI, GFR, HTN, DM, and smoking. Adjustment for age, race, and GFR completely attenuated the borderline univariable association among SLE subjects. Hcy and disease duration (factors previously identified to be associated with CAC in SLE) did not alter these findings (data not shown).

Resistin and medications. Details of medication use between SLE subjects and controls was previously published⁵. Briefly, SLE subjects taking prednisone ($p = 0.018$), beta-blockers ($p = 0.005$), and ACE inhibitors ($p = 0.024$) had higher resistin levels. However, medications such as statins, ASA, hydroxychloroquine, cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate did not show a correlation with higher resistin levels (data not shown).

DISCUSSION

We have shown that resistin concentrations are higher in female subjects with SLE than in age and race-matched controls, independent of factors including age, race, BMI, GFR, hsCRP, HTN, DM, and steroid use. Our findings are in con-

Table 2. Spearman correlations between resistin levels and other measured variables among SLE subjects and controls.

Variable	SLE		Controls	
	Rho	p	Rho	p
Age	0.048	0.6	-0.19	0.1
BMI, kg/m ²	-0.060	0.5	0.13	0.3
GFR, ml/min/1.75 m ²	-0.32	< 0.0001	0.14	0.3
Homocysteine, μ mol/l	0.37	< 0.0001	-0.21	0.08
Albumin, g/dl	-0.27	0.003	-0.18	0.3
Triglycerides, ng/ml	0.21	0.008	0.022	0.9
LDL, ng/ml	-0.11	0.2	0.046	0.7
HDL, ng/ml	-0.19	0.02	-0.12	0.3
Uric acid	0.26	0.02	0.32	0.04
hsCRP	0.32	0.0001	0.21	0.07
Disease-specific				
Average prednisone dose	0.16	0.05	NA	—
Disease duration	0.18	0.02	NA	—
ESR	0.19	0.02	NA	—
SLICC-DI	0.27	0.0006	NA	—
SLEDAI	0.11	0.1	NA	—
Insulin resistance				
Fasting glucose	-0.14	0.9	0.0073	0.9
HOMA	0.064	0.5	0.034	0.8
QUICKI	0.064	0.5	-0.034	0.8
Insulin level	-0.10	0.2	0.044	0.7
HgbA1c	0.053	0.8	NA	—
Coronary calcification				
Calcium score	0.11	0.2	0.049	0.7

LDL: low-density lipoprotein; HDL: high-density lipoprotein; QUICKI: quantitative insulin sensitivity check index; NA: not applicable; other abbreviations as in Table 1.

trast to 2 previous studies showing no difference in resistin levels between SLE subjects and controls^{22,23}. This may be the result of different sample sizes and to the greater severity of disease in our SLE population.

In our study, measures of inflammation, disease damage, and renal dysfunction correlated most clearly with resistin level among patients with SLE. In contrast, associations with inflammatory markers (hsCRP, Hcy) and GFR did not correlate with resistin levels among controls. Among controls, GFR and Hcy tended toward an association with resistin that was in the opposite direction from subjects with SLE. Testing for effect modification indeed identified that this difference was significant and suggests that these associations may be different in SLE subjects and in controls. Similarly, BMI was lower among SLE subjects with high resistin levels, while this was the opposite among controls. These findings could suggest different mechanisms for elevations in resistin among patients with SLE compared to controls without autoimmune disease.

Unexpectedly, among SLE subjects, resistin levels did not correlate with the HOMA, a measure of insulin resistance. Resistin did not correlate with BMI, insulin levels, fasting glucose, HOMA, or a diagnosis of diabetes, suggesting that this finding is not a false-negative. There was also no difference in the HOMA between patients with SLE and controls. However, the lack of an expected difference in the insulin resistance of cases vs controls may simply indicate that our sample size was too small to detect subtle differences in glucose metabolism. We did see a correlation

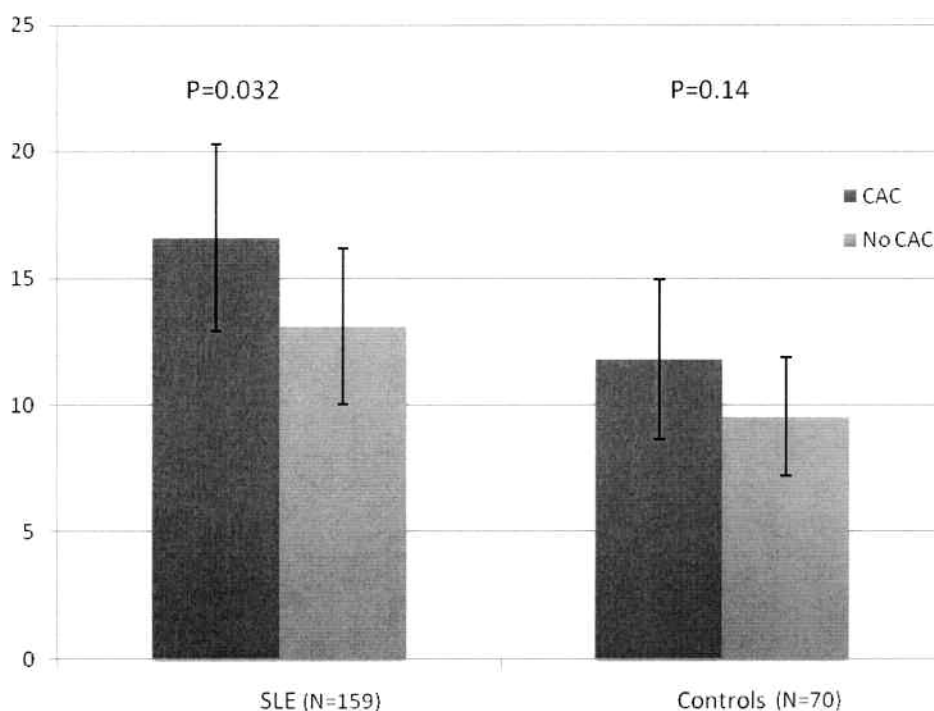


Figure 1. Resistin levels in subjects with SLE and controls by coronary artery calcification (CAC) status.

Table 3. Multivariable analysis evaluating the association between resistin levels (per 1 ng/ml or greater than the median value of 10 ng/ml) and the presence of coronary artery calcification.

Resistin	OR (95% CI)	p
SLE*		
Per 1 ng/ml	1.03 (1.00–1.07)	0.06
Over 10 ng/ml	1.40 (0.66–2.99)	0.3
SLE†		
Per 1 ng/ml	1.02 (0.97–1.06)	0.5
Over 10 ng/ml	0.93 (0.38–2.24)	0.9
Controls*		
Per 1 ng/ml	1.04 (0.95–1.14)	0.4
Over 10 ng/ml	1.78 (0.42–7.44)	0.4
Controls†		
Per 1 ng/ml	1.04 (0.93–1.16)	0.5
Over 10 ng/ml	1.75 (0.32–9.68)	0.5

* Adjusted for age and race. † Adjusted for age, race, body mass index, glomerular filtration rate, hypertension, diabetes, and smoking. SLE: systemic lupus erythematosus.

between resistin and some components of the metabolic syndrome (triglycerides, HDL, uric acid), and thus visceral fat and the metabolic syndrome may still be associated with resistin levels in SLE, despite the lack of association with measures of glucose metabolism and insulin resistance. Alternatively, these observations may simply be markers of more severe disease or greater use of corticosteroids. Quantification of visceral fat may help clarify its role in future studies.

We hypothesize that resistin is elevated in patients with SLE, independent of its association with insulin resistance through an association with inflammation and organ dysfunction, particularly renal dysfunction. This has been previously described in critically ill patients³⁸. Resistin has previously been associated with inflammation and renal disease in patients with SLE¹⁹ and was strongly correlated with ESR, hsCRP, Hcy, and renal disease in our study.

It is unclear how markers of inflammation and end-organ damage may be related to resistin levels. Renal dysfunction has been associated with elevated resistin levels^{39,40,41}, although in our study SLE was associated with higher resistin levels, independent of GFR. In addition, CRP and Hcy have recently been shown to upregulate resistin production from peripheral blood mononuclear cells and adipocytes, respectively^{18,42}. Thus inflammation may directly affect an increase in resistin levels. The mechanism by which resistin is increased in patients with SLE remains unknown, but postulated explanations include changes in renal function, direct effects of inflammatory mediators on resistin production, alterations in fat distribution, or some combination of these mechanisms.

Resistin levels were also higher in patients with SLE who had CAC compared to those without CAC, although this appears to be explained by an association between resistin

and other, previously defined risk factors for CAC in this population. While resistin levels were higher in patients with SLE who had evident CAC, there was no clear correlation between resistin and calcium score and the borderline association in regression was dependent on other variables such as age and GFR. Thus, any association between resistin and CAC may be confounded by associations with other risk factors, particularly renal dysfunction. A small association between resistin and CAC among SLE subjects or controls cannot be ruled out with our sample size. Our results do not support resistin as an independent risk factor for ASCVD in persons with SLE.

This study has several limitations. First, our sample size was not large enough to rule out a small association between resistin and CAC. Second, we did not have measurements of waist circumference, which limited the study of a potential association between resistin and metabolic syndrome and abdominal obesity. Finally, although we determined that SLE is associated with elevated resistin levels, our study did not address the clinical importance of this finding, which remains unclear. Our study was cross-sectional and did not address questions of causality or longitudinal change. Further study is needed to better characterize the role of resistin in SLE, particularly with regard to the development of ASCVD.

Our data show that resistin was independently elevated in patients with SLE compared to age and race-matched controls. Resistin levels correlated with measures of disease severity, inflammation, renal dysfunction, and markers of renal dysfunction among patients with SLE. This suggests alternative mechanisms for elevation of resistin among patients with SLE that are not associated with insulin resistance or obesity. Elevated resistin concentrations were found in SLE subjects with increased CAC but this association was dependent on other established risk factors, most notably GFR.

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