Published in final edited form as:

J Rheumatol. 2011 November ; 38(11): 2369–2375. doi:10.3899/jrheum.110237.

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

Joshua F. Baker, MD¹, Megan Morales¹, Mohammed Qatanani, MD³, Andrew Cucchiara, PhD², Eleni Nackos, MD¹, Mitchell A. Lazar, MD, PhD³, Karen Teff, PhD³, and Joan Marie Von Feldt, MD, MEd¹

¹Division of Rheumatology, Department of Medicine, University of Pennsylvania

²Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania

³Division of Endocrinology, Diabetes & Metabolism, University of Pennsylvania

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 female SLE subjects and 70 age and race-matched 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 positively correlated with SLICC Damage Index, GFR, hsCRP, ESR, 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 v. 13.10 ng/ml, $p = 0.04$). However, in multivariate logistic regression, the association not present after adjustment for age, race, and GFR.

Conclusion—SLE was independently associated with higher resistin levels. Among SLE, higher resistin 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.

Key Indexing Terms

resistin; systemic lupus erythematosus; atherosclerosis; insulin resistance

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease, which occurs predominantly in women(1, 2). Individuals with SLE have a greater risk of developing premature atherosclerotic cardiovascular disease (ASCVD) than the general population(3). Factors that are 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 independently of known risk factors(4). We have shown that hyperhomocysteinemia and disease duration are associated with the presence of coronary artery calcification (CAC) in SLE patients, as determined by Electron Beam Computed Tomography (EBCT)(5). Additional biomarkers to identify premature ASCVD in SLE continue to be sought.

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 TNF- α , IL-6 and C-reactive peptide as well as Monocyte Chemoattractant Protein (MCP-1)(8–11). It is thought that 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(12–14).

Adipokines, which are factors released from adipocytes, stimulate inflammatory activity which may be involved in the etiology of insulin resistance. Resistin, a recently identified adipokine, has been found to be elevated in obese and insulin resistant rodents and humans(15). In rodents, resistin is made exclusively by adipocytes, whereas in humans, resistin is made primarily in macrophages(16). In humans, resistin is also induced by acute inflammatory stimuli(17) and has pro-inflammatory properties. In vitro studies suggest that homocysteine (Hcy), elevated in inflammatory states, may impair the insulin signaling pathway and induce an increase in resistin expression(18). Resistin has also been shown to be elevated in SLE in one study, and to correlate with markers of inflammation, glomerular filtration rate (GFR), and steroid use(19). Alterations in resistin have also been found in other autoimmune diseases, such as Sjogren's syndrome and ankylosing spondylitis(20, 21). In contrast, several other studies have shown no difference in resistin levels among SLE compared to controls(22–24).

In the general population, resistin has been associated with atherosclerosis. Reilly et al. 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 90 diabetics, resistin levels were higher among those with coronary artery disease(25). In subjects recently suffering a

myocardial infarction, or undergoing percutaneous coronary interventions, resistin levels correlate with severity of coronary atherosclerosis and predict further events(26–28).

We evaluated resistin levels and measures of insulin resistance in a previously described (5) case cohort study of female SLE subjects and age and race-matched controls in order to determine 1) if resistin levels are elevated in SLE and 2) 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.

Methods

Study Subjects

Consecutive, nonpregnant, female SLE patients over the age of 18 (n = 159) and age (± 2 years) and race-matched non-pregnant female controls 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 previously published(5). SLE patients were required to fulfill at least four of the American College of Rheumatology revised criteria for the classification of SLE(22). The study was approved by the Institutional Review Board of the University of Pennsylvania, and written informed consent was obtained from each participant. In this sub-study, stored serum was sent for measurement of resistin levels on all SLE patients (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, a fasting blood sample drawn, and underwent EBCT as previously described(5). Clinical characteristics have been previously reported(5, 29).

We used a modified version of the International Diabetes Federation definition of the metabolic syndrome(30). Waist circumference was not available, thus metabolic syndrome was considered present in an obese patient (BMI>30) with any 2 of the following: 1) an elevated TG level greater than 150 mg/dL, 2) an HDL level <40 mg/dL in males and <50 mg/dL in females, 3) a 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, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), total cholesterol, triglycerides, fibrinogen, creatinine, Westergren erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), MCP-1, anti-double-stranded DNA (dsDNA), and complement C3 and C4. Estimated GFR was estimated for each subject using the Modification of Diet in Renal Disease equation(26). Total plasma Hcy

concentrations were determined using the AxSYM Homocysteine via Fluorescence Polarization Immunoassay (Abbot Laboratories, Abbot Park, IL). Insulin levels were determined using a human insulin specific radioimmunoassay (Linco Research, St. Charles, Missouri, United States). Insulin resistance was estimated using the Homeostatic model assessment (HOMA), which is calculated using the formula (fasting insulin * fasting glucose)/ 22.5). Resistin concentrations in stored plasma were assessed with a commercially available ELISA (Linco Research, St. Charles, Missouri, United States). The within assay variation for this assay is between 3.8% and 7.0% and the between assay variation is between 7.1 and 7.7%.

Electron Beam Computed Tomography

CAC appears in the very early stages of ASCVD and progresses with the disease; furthermore, CAC scores determined by EBCT reflect total atherosclerotic burden and are predictive of future cardiac events(31).

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) for 2 image acquisitions. Serial, contiguous, 3-mm-thick transverse images 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) as previously described (5). Data were quantitatively scored in a blinded manner by a registered radiology technologist. Scores were calculated using the method described by Agatston et al(32). Total CAC was quantified by summing across the 4 major epicardial arteries, resulting in a raw CAC [rCAC] score. These scores were compared with rCAC scores from a previously established population of (age- and sex- matched) individuals whose data were preprogrammed as the control standard.

Statistical Analysis

Data was analyzed on STATA 11 software. A two-tailed p-value < 0.05 was the criterion for statistical significance. Graphical displays (e.g. histograms, boxplots and scatter-plots) were used to examine distributions, guide data transformations as needed, and assess bivariate relations. T-tests and ranksum 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 values(33). 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 previously 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 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 and controls, we evaluated for interaction between the diagnosis of SLE and these variables.

Univariable and multivariable logistic regression analysis 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. Pre-determined traditional risk factors for CAC were evaluated as potential confounders including age, race, GFR, DM, HTN, and smoking. Separately, we also evaluated homocysteine 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 previously been reported(5). Briefly, SLE subjects 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 versus 93.6; $p = 0.07$). Significantly more SLE subjects than controls were treated with prednisone, β -blockers, and anti-depressants, in addition to immunosuppressive therapies (data not shown). Treatment with statins and aspirin did not differ significantly between SLE and controls. This sample population represented significantly higher percentage of self-reported diabetics in the SLE group than the control group (10.3% v. 3.0%, $p=0.025$), although the BMI of the two groups was found to be similar (28.48 v. 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 (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 which included age, race, BMI, GFR, hsCRP, HTN, and diabetes (β : 0.19 (-0.0084, -0.37) $p=0.040$). The adjusted mean resistin level among SLE was 12.0 ng/mL, while the adjusted mean among controls was 9.3 ng/mL. When steroid use (past, present, or never) was included in the model, this association was similar (β : 0.19 (-0.0054, -0.37) $p=0.044$). Separately, controlling for the presence of the metabolic syndrome and homocysteine levels did not significantly attenuate the association. Furthermore, adjustment for the use of statins, aspirin, and ACE-inhibitors also did not attenuate the association (data not shown).

Resistin and Factors Associated with SLE

SLE patients with 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* homocysteine ($p=0.06$) level. Factors that are traditionally associated with disease in SLE patients 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 SLICC-DI were all found to have a significant correlation with resistin levels (Table 2). However, the SLE-DAI was not found to significantly associate with resistin levels in SLE patients. When the associated variables from Table 2 were included in predictive multivariable linear regression model, independent predictors of a log-transformed resistin level in SLE included GFR, ESR, and Hcy in a model that also included age, race, BMI, DM and HTN.

The association between resistin and GFR, homocysteine, and BMI appeared qualitatively different in Table 2. Therefore, we tested for interaction to determine if the associations between these variables and resistin were statistically different between SLE and controls in a model which 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 homocysteine and resistin ($p=0.02$). There was no significant interaction between BMI and the diagnosis of SLE on resistin levels.

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 between subjects with high and low resistin levels. Resistin levels were not significantly higher in controls with metabolic syndrome (13.0 ± 11.5 ng/mL v. 9.5 ± 5.6 ng/mL $p=0.15$), or in subjects with SLE and metabolic syndrome (14.1 ± 11.5 v. 12.2 ± 9.1 $p=0.31$).

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 v. 13.10 ng/mL, $p=0.032$) (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 a significantly higher resistin concentrations compared with controls who did not have CAC (11.80 v. 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 resistin level in SLE subjects and controls. Resistin did not associate with the presence of CAC in either group after adjusting 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 (previously identified factors associated with CAC in SLE) did not alter these findings (data not shown).

Resistin and Medications

Details of medication use between SLE and controls has been previously published(5). Briefly, SLE subjects taking prednisone ($p = 0.018$), β -blockers ($p = 0.005$), and ACE inhibitors ($p = 0.024$) had higher resistin levels. However, medications such as statins, ASA, hydroxychlorquine, cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate did not demonstrate 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 a number of factors including age, race, BMI, GFR, hsCRP, HTN, DM, and steroid use. Our findings are in contrast to two previous studies showing no difference in resistin levels between SLE 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 most clearly correlated with resistin 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 towards an association with resistin in the *opposite direction* as in subjects with SLE. Testing for effect modification indeed identified that this difference was significant and suggests that these associations may be different in SLE and in controls. Similarly, BMI was lower among SLE subjects with high resistin levels, whereas 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, 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 SLE patients and controls. However, the lack of an expected difference in the insulin resistance of cases versus controls may simply indicate that our sample size was too small to detect subtle differences in glucose metabolism. We did see a correlation between resistin and some components of the metabolic syndrome (TG, 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 patients(34). Resistin has previously been associated with inflammation and renal disease in patients with SLE(19) 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(35–37), though 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 PBMC and adipocytes, respectively(18, 38). 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: a) changes in renal function, b) direct effect of inflammatory mediators on resistin production, c) alterations in fat distribution, or some combination of one or more of these mechanisms.

Resistin levels were also higher in SLE patients with 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 or controls cannot be ruled out with our sample size. Our study does not support resistin as an independent risk factor for ASCVD in SLE.

This study has several limitations. Firstly, as stated, our sample size is not large enough to rule out a small association between resistin and CAC. Secondly, 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, though we have determined that SLE is associated with elevated resistin levels, our study does not address the clinical importance of this finding, which remains unclear. Our study is cross-sectional and does 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.

In conclusion, our data show that resistin is independently elevated in patients with SLE when compared to controls. Resistin levels correlate with measures of disease severity, inflammation, renal dysfunction, and markers of renal dysfunction among patients with SLE.. This suggests alternative mechanisms for resistin elevation among 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.

Acknowledgments

This investigation was supported (in part) by: Lupus Research Institute, The Clinical and Translational Research Center of the University of Pennsylvania through a Public Health Services Research Grant M01 RR00040 from the National Institutes of Health and The Diabetes and Endocrinology Research Center Sponsored by NIH DK 19525

References

1. Westerweel PE, Luyten RK, Koomans HA, Derksen RH, Verhaar MC. Premature atherosclerotic cardiovascular disease in systemic lupus erythematosus. *Arthritis Rheum.* 2007 May; 56(5):1384–96. [PubMed: 17469095]
2. Simard JF, Costenbader KH. What can epidemiology tell us about systemic lupus erythematosus? *Int J Clin Pract.* 2007; 61(7):1170–80. [PubMed: 17577298]
3. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA, al LJ-Me. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol.* 1997; 145(5):408–15. [PubMed: 9048514]
4. Esdaile J, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, Berger RD, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum.* 2001; 44(10):2331–7. [PubMed: 11665973]
5. Von Feldt JM, Scalzi LV, Cucchiara AJ, Morthala S, Kealey C, Flagg SD, et al. Homocysteine levels and disease duration independently correlate with coronary artery calcification in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2006 Jul; 54(7):2220–7. [PubMed: 16802358]
6. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest.* 2003 Dec; 112(12):1785–8. [PubMed: 14679172]
7. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest.* 2003 Dec; 112(12):1821–30. [PubMed: 14679177]
8. Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysoshoou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. *Atherosclerosis.* 2005 Dec; 183(2):308–15. [PubMed: 16285994]
9. McLaughlin T, Abbasi F, Lamendola C, Liang L, Reaven G, Schaaf P, et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. *Circulation.* 2002 Dec 3; 106(23):2908–12. [PubMed: 12460870]
10. Guldiken S, Demir M, Arikan E, Turgut B, Azcan S, Gerenli M, et al. The levels of circulating markers of atherosclerosis and inflammation in subjects with different degrees of body mass index: Soluble CD40 ligand and high-sensitivity C-reactive protein. *Thromb Res.* 2007; 119(1):79–84. [PubMed: 16476470]
11. Dahlman I, Kaaman M, Olsson T, Tan GD, Bickerton AS, Wahlen K, et al. A unique role of monocyte chemoattractant protein 1 among chemokines in adipose tissue of obese subjects. *J Clin Endocrinol Metab.* 2005 Oct; 90(10):5834–40. [PubMed: 16091493]
12. Ryan MJ, McLemore GR Jr, Hendrix ST. Insulin resistance and obesity in a mouse model of systemic lupus erythematosus. *Hypertension.* 2006 Nov; 48(5):988–93. [PubMed: 16982954]
13. Sada KE, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, Maeshima Y, et al. Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. *J Rheumatol.* 2006 Aug; 33(8):1545–52. [PubMed: 16881111]
14. Escarcega RO, Garcia-Carrasco M, Fuentes-Alexandro S, Jara LJ, Rojas-Rodriguez J, Escobar-Linares LE, et al. Insulin resistance, chronic inflammatory state and the link with systemic lupus erythematosus-related coronary disease. *Autoimmun Rev.* 2006 Nov; 6(1):48–53. [PubMed: 17110317]
15. Barnes KM, Miner JL. Role of resistin in insulin sensitivity in rodents and humans. *Curr Protein Pept Sci.* 2009 Feb; 10(1):96–107. [PubMed: 19275676]
16. Qatanani M, Szwergold NR, Greaves DR, Ahima RS, Lazar MA. Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. *J Clin Invest.* 2009 Feb 22(37273)
17. Lu SC, Shieh WY, Chen CY, Hsu SC, Chen HL. Lipopolysaccharide increases resistin gene expression in vivo and in vitro. *FEBS Lett.* 2002 Oct 23; 530(1–3):158–62. [PubMed: 12387885]
18. Li Y, Jiang C, Xu G, Wang N, Zhu Y, Tang C, et al. Homocysteine upregulates resistin production from adipocytes in vivo and in vitro. *Diabetes.* 2008 Jan 11.
19. Almehed K, Forsblad Delia H, Bokarewa M, Carlsten H. Role of resistin as a marker of inflammation in SLE. *Arthritis Res Ther.* 2008 Jan 30.10(1):R15. [PubMed: 18234104]

20. Bostrom EA, d'Elia HF, Dahlgren U, Simark-Mattsson C, Hasseus B, Carlsten H, et al. Salivary resistin reflects local inflammation in Sjogren's syndrome. *J Rheumatol*. 2008 Oct; 35(10):2005–11. [PubMed: 18709689]
21. Kocabas H, Kocabas V, Buyukbas S, Melikoglu MA, Sezer I, Butun B. The serum levels of resistin in ankylosing spondylitis patients: a pilot study. *Rheumatol Int*. 2010 Dec.8:8.
22. Chung CP, Long AG, Solus JF, Rho YH, Oeser A, Raggi P, et al. Adipocytokines in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. *Lupus*. 2009 Aug; 18(9):799–806. [PubMed: 19578104]
23. De Sanctis JB, Zabaleta M, Bianco NE, Garmendia JV, Rivas L. Serum adipokine levels in patients with systemic lupus erythematosus. *Autoimmunity*. 2009 May; 42(4):272–4. [PubMed: 19811274]
24. Vadacca M, Margiotta D, Rigon A, Cacciapaglia F, Coppolino G, Amoroso A, et al. Adipokines and systemic lupus erythematosus: relationship with metabolic syndrome and cardiovascular disease risk factors. *J Rheumatol*. 2009 Feb; 36(2):295–7. [PubMed: 19132788]
25. Liu D, Manske SL, Kontulainen SA, Tang C, Guy P, Oxland TR, et al. Tibial geometry is associated with failure load ex vivo: a MRI, pQCT and DXA study. *Osteoporosis International*. 2007; 18:991–7. [PubMed: 17268944]
26. Wang H, D DYC, Cao J, He ZY, Zhu BP, Long M. High serum resistin level may be an indicator of the severity of coronary disease in acute coronary syndrome. *Chin Med Sci J*. 2009 Sep; 24(3): 161–6. [PubMed: 19848317]
27. Momiyama Y, Ohmori R, Uto-Kondo H, Tanaka N, Kato R, Taniguchi H, et al. Serum resistin levels and cardiovascular events in patients undergoing percutaneous coronary intervention. *J Thromb*. 2011 Feb 24; 18(2):108–14. 2010. Epub 2010 Nov 6.
28. Lee SH, Ha JW, Kim JS, Choi EY, Park S, Kang SM, et al. Plasma adiponectin and resistin levels as predictors of mortality in patients with acute myocardial infarction: data from infarction prognosis study registry. *Coron Artery Dis*. 2009 Jan; 20(1):33–9. [PubMed: 18997620]
29. Brown KS, Nackos E, Morthala S, Whitehead AS, Feldt JMV. Monocyte chemoattractant protein-1: plasma concentrations and A(-2518)G promoter polymorphism of its gene in systemic lupus erythematosus. *J Rheumatol*. 2007 Apr; 34(4):740–6. [PubMed: 17407231]
30. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med*. 2006; 23(5):469–80. [PubMed: 16681555]
31. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol*. 2005; 46(1):158–65. [PubMed: 15992651]
32. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990 Mar 15; 15(4):827–32. [PubMed: 2407762]
33. Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. *Clin Chem*. 2004; 50(9): 1511–25. [PubMed: 15265818]
34. Koch A, Gressner OA, Sanson E, Tacke F, Trautwein C. Serum resistin levels in critically ill patients are associated with inflammation, organ dysfunction and metabolism and may predict survival of non-septic patients. *Crit Care*. 2009; 13(3):R95. [PubMed: 19545363]
35. Yaturu S, Reddy RD, Rains J, Jain SK. Plasma and urine levels of resistin and adiponectin in chronic kidney disease. *Cytokine*. 2007 Jan; 37(1):1–5. [PubMed: 17383891]
36. Malyszko J, Malyszko JS, Pawlak K, Mysliwiec M. Resistin, a new adipokine, is related to inflammation and renal function in kidney allograft recipients. *Transplant Proc*. 2006 Dec; 38(10): 3434–6. [PubMed: 17175295]
37. Taskapan MC, Taskapan H, Sahin I, Keskin L, Atmaca H, Ozyalin F. Serum leptin, resistin, and lipid levels in patients with end stage renal failure with regard to dialysis modality. *Ren Fail*. 2007; 29(2):147–54. [PubMed: 17365928]
38. Hu WL, Qian SB, Li JJ. Decreased C-reactive protein-induced resistin production in human monocytes by simvastatin. *Cytokine*. 2007 Dec; 40(3):201–6. [PubMed: 18023360]

Figure 1.
Resistin levels in SLE and controls by CAC status.

Table 1

Baseline characteristics of SLE and controls by resistin level (above or below the median value). Values are displayed as mean(SD) or median(IQR) if skewed.

Variable	All Participants	Resistin>10 ng/mL	Resistin <=10 ng/mL	P value
SLE				
N	159	85	74	N/A
Age (yrs)	43.2 (11.1)	43.6 (11.2)	42.6 (11.1)	0.7
Caucasian, %	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/1.75m 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/hr)	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
SLE-DAII	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	N/A
Age (years)	44.8 (9.8)	41.6 (9.0)	46.8 (9.9)	0.03
Caucasian, %	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/1.75m 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

Variable	All Participants	Resistin>10 ng/mL	Resistin <=10 ng/mL	P value
Metabolic Syndrome, %	11.4	11.1	11.6	0.9

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

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

Variable	SLE		Controls	
	Rho	P-value	Rho	P value
Age	0.048	0.6	-0.19	0.1
BMI (kg/m ²)	-0.060	0.5	0.13	0.3
GFR (mL/min/1.75m ²)	-0.32	<0.0001	0.14	0.3
Homocysteine (μmol/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				
Avg. Prednisone Dose	0.16	0.05	N/A	–
Disease Duration	0.18	0.02	N/A	–
ESR	0.19	0.02	N/A	–
SLICC-DI	0.27	0.0006	N/A	–
SLE-DAI	0.11	0.1	N/A	–
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	N/A	–
CORONARY CALCIFICATION				
Calcium Score	0.11	0.2	0.049	0.7

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	Odds Ratio	95% CI	P value
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, race.

† Adjusted for age, race, BMI, GFR, HTN, DM, and smoking.