Resistin, an adipokine, its relation to inflammation in Systemic Lupus Erythematosus and Rheumatoid Arthritis

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ABSTRACT

Objective: To determine the difference in serum resistin levels in Systemic lupus Erythematosus (SLE) and Rheumatoid arthritis (RA) patients compared to a control group. Also, to find the relationship between serum resistin levels and disease activity in SLE and RA patients.

Subjects and Methods: This study included three groups of 30 SLE patients, 30 RA patients and 30 apparent healthy volunteers. All patients were subjected to full history taking, clinical examination, laboratory assessment (ESR, CRP, renal function, urine examination, lipid profile, RF, ANA, anti-dsDNA, ACPA, C3 and C4), X-ray both hands for RA patients for both SLE and RA patients, assessment of disease activity according to SLEDAI for SLE patients and according to DAS 28 score for RA patients and assessment of radiological damage for RA patients using Larsen score. Serum samples from all patients and controls were tested for serum resistin levels.

Results: The mean of serum resistin levels in SLE (2.86±0.02 ng/ml) and RA (3.002±0.06 ng/ml) were insignificantly higher than controls (2.14± 0.08ng/ml) ($p=0.233$ and $p=0.07$ respectively) . There was no significant difference between serum resistin levels between SLE and RA patients ($p=0.586$). There were insignificant correlations between disease duration and all laboratory parameters compared to serum resistin levels in SLE and RA ($p>0.05$) but the platelets had an inverse significant correlation with serum resistin levels in SLE ($p<0.022$). There was insignificant correlation between serum levels of resistin and SLEDAI in SLE ($p=0.180$). Moreover, there was insignificant correlation between and DAS 28 and Larsen score compared to serum resistin levels in RA ($p=0.207$, $p=0.735$, respectively).

Conclusion: Serum resistin levels did not correlate with clinical or laboratory markers except platelet counts in SLE and or RA cases, although it is a higher level in these diseases compared to the controls.

Key words: Resistin, SLE and RA.

Introduction

Systemic Lupus Erythematosus (SLE) is a disease characterized by systemic inflammation with the property of affecting several organs throughout the body (1). Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disorder of unknown etiology that primarily affects the synovial lining of the diarthrodial joints. It is characterized by symmetric, erosive synovitis and in some cases extra-articular involvement (2); most patients experience a chronic fluctuating course of disease that, despite therapy, may result in progressive joint destruction, deformity, disability, and even premature death (3).

Resistin is a low-molecular-weight adipokine also known as the adipocyte specific secretory factor that was independently identified by three groups (4). It is an adipocyte secreted hormone belonging to a cysteine-rich protein family. It is expressed in white adipose tissues in rodents and has also been found in several other tissues in humans. Insulin, glucose, many cytokines and anti-diabetic thiazolidinediones are regulators of resistin gene expression (5).

The role of resistin in humans has not been fully established (6). It was first proposed to be involved in insulin resistance and type 2 diabetes, but later, it was found to be relevant to inflammation and inflammation-related diseases like atherosclerosis and arthritis (5). There was evidence that resistin has proinflammatory properties, is abundant in inflammatory diseases e.g., RA and Crohn's disease; and is also associated with inflammatory markers in several different populations (7, 8).

Resistin was found accumulated in inflamed joints of patients with RA and had the capacity to induce arthritis in mice. In humans, resistin is expressed in inflammatory cells, leukocytes, and macrophages and has the potency of inducing production of interleukin -6 and tumor necrosis factor-alpha (9, 10).

Aim of the Work

The aim of this work is to determine the level of resistin in the serum of patients with SLE and RA. The aim extends to examine the relationship and possible associations between the serum resistin levels and different markers of disease activity, inflammation, renal function and lipids with RA and SLE patients.

Subjects and Methods

Thirty patients fulfilling at least four of the updated American College of Rheumatology (ACR) revised criteria for the classification of systemic lupus erythematosus (SLE) (11), thirty patients fulfilling at least four of the 1987 Revised ACR Criteria for the classification of rheumatoid arthritis (RA (12) and 30 apparent healthy volunteers matched for age and sex with the SLE and RA were enrolled in this study.

These patients were recruited from the in-patients and out-patients' clinic of the Rheumatology, Rehabilitation and Physical Medicine Department of King Fahad Specialist Hospital Dammam Saudi Arabia. Informed consent was obtained from all participants, and the study was approved by the IRB committee of King Fahad Specialist Hospital Dammam.

Patients with the following conditions were excluded from the study including pre-existing diseases causing nephritis, evidence of malignancy, concurrent infection and diabetes in patients and controls.

All the patients and controls were subjected to complete history taking as well as thorough clinical examination. Assessment of disease activity of SLE was done using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (13). Grading of SLE disease activity (SLEDAI) includes Mild activity: 1-10, Moderate activity: 11-20, Severe activity: 21-45, Very severe activity: >45 (13).

Assessment of the Disease Activity Score 28 (DAS28) was done in patients with RA (14). The rheumatoid Disease Activity Score 28 (DAS28) was determined from scores as follows: Remission: DAS 28 $\leq$ 2.6, Low disease activity: DAS 28 >2.6 $\leq$ 3.2, Moderate disease activity: DAS 28 > 3.2 and $\leq$ 5.1, High disease activity: DAS 28 > 5.1. DAS 28 = [0.56 × $\sqrt{}$ (tender 28) + 0.28 × $\sqrt{}$ (swollen 28) + 0.70 × Ln (ESR)] 1.08 + 0.16 (14).

All patients were subjected to the following lab tests as indicated by their disease, using standard laboratory techniques Erythrocyte Sedimentation Rate [ESR] by Westergren method, C-reactive protein (CRP) by latex agglutination slide test, serum creatinine and blood urea, complete urine analysis, complete blood count, C3 & C4 by using a standard nephelometric technique, ANA by using a standard immune-fluorescence technique, Anti double stranded DNA by using ELISA testing and Plasma lipoproteins by using a standard colorimetric reaction.

Serum resistin levels were determined in patients and controls by using a quantitative sandwich Enzyme-Linked Immunosorbent Assay (ELISA). 2 ml venous blood samples are taken after a one-night fast, and serum from these samples will be stored at -70°C until the time of analyses according to a standard ELISA technique using a Quantikine ELISA kit for Human Resistin supplied by R&D Systems USA.

Plain X-ray of both hands and wrists, postero-anterior views, were done for all RA patients. Radiographic damage specific for RA is evaluated by Larsen method (LS) for each of the patients (15).

Statistical analysis was performed using an IBM computer utilizing Statistical Package for Social Science (SPSS) program version 16. Continuous data were expressed in the form of mean ±SD while categorical data were expressed in the form of count and percent. The difference between the two groups was analyzed via student's t-test. One-way analysis of variance (ANOVA) was used to compare more than two groups. Spearman's correlation coefficient (r) was used to assess the degree of association between 2 continuous variables.

Results

Table 1: Demographic characteristics, clinical and Laboratory data in SLE and RA patients and control (ANOVA test)

Mean ±SD	SLE	RA	Controls
Age (years)	40.36±10.55 p1> 0.05	40.24± 10.41 p2> 0.05	38.07±10.01
Sex	All Females	All Females	All Females
BMI kg/m2	32.05±1.07 p1> 0.05	29.48± 1.11 p> 0.05	30.17± 1.01
Disease duration (y)	9.73± 6.78 p1> 0.05	6.1± 3.7 p> 0.05	-
SLEDAI score	4.63 ±0.4 p1> 0.05	-	-
DAS 28 score	-	4.19 ±0.2 p2> 0.05	-
Larsen score	-	1.5 ±0.02 p2> 0.05	-
ESR mm/1st hour	33.76± 7.2 p1> 0.05	47.5± 8.5 P2> 0.05	15.23±5.3
CRP mg/l	10.2± 2.3 p1> 0.05	26.43±2.7 p 2> 0.05	7.9±1.8
HB gm%	10.7± 2.1 p1> 0.05	10.7±2.4 p 2> 0.05	8.1±1.7
RBCs thousands/ mm3	4.76± 0.4 p1> 0.05	4.484± 0.6 p2> 0.05	3.64±0.8
WBCs thousands/ mm3	7.08±2.2 p1> 0.05	7.96 ±2.8 p2> 0.05	5.88±2.2
Platelet thousands/ mm3	294.43 ±74.3 p1> 0.05	366.83 ±63.2 **p 2< 0.05***	265±53.1
Total cholesterol mmol/l	6.18 ±1.7 p1> 0.05	6.71 ±1.9 p2> 0.05	3.69±1.5
TG mmol/l	1.21± 0.08 p1> 0.05	1.224 ±0.05 p2> 0.05	0.4±0.01
Serum create nine µmol/l	160.93 ±10.7 p1> 0.05	71.73±10.4 p2> 0.05	39.34±7.7
Anti-dsDNA IU/ml	80.03 ±13.9 p1> 0.05	-	12.9±3.75
C3 g/l	1.14± 0.01 p1> 0.05	-	0.50±0.08
C4 g/l	0.26±0.05 p1> 0.05	-	0.02±0.009
Serum Resistin , ng/ml	2.86± 0.02 p1> 0.05	3.00±0.06 p2> 0.05	2.41 ±0.08

• Relation between two groups of SLE and RA patients and control group,

• p 1= between SLE patients and control, p 2= between RA patients and controls.

• Non-Significant (NS) p > 0.05; Significant (S) * p < 0.05

The mean of serum resistin levels in SLE (2.866 ng/ml) and RA (3.002 ng/ml) were insignificantly higher than controls (2.14 ng/ml) (p=.233 and p=.233 respectively). There was no significant difference between serum levels of resistin between SLE and RA parients (p=0.098). There were insignificant correlations between disease duration and all laboratory parameters compared to serum resistin levels in SLE and RA (p>0.05) but the platelets had an inverse significant correlation with serum resistin levels in SLE (p< 0.022). There was insignificant correlation between serum levels of resistin and SLEDAI in SLE (p=0.180).

There was insignificant correlation between DAS 28 and Larsen score compared to serum levels of resistin in RA (p=0.207, p=0.735, respectively) (p>0.05). The demographic characteristics, clinical and laboratory findings of all the studied groups are demonstrated in Table 1. Table 2 shows correlations of serum resistin levels with clinical and laboratory data in SLE and RA patients. While, Table 3 and Figure 1 reveal correlation of serum resistin levels in SLE, RA patients and controls.

Table 2: Correlations of serum resistin levels with clinical and laboratory data in SLE and RA patients

Parameter	Serum resistin levels correlation coefficients *(r)* in SLE patients	Serum resistin levels correlation coefficients *(r)* in RA patients
Age	*(r)*-0.176,P=0.617	*(r)*-0.081,P=0.742
Disease duration	*(r)*0.090 ,P=0.779	*(r)*0.576 ,P=0.499
BMI	*(r)*0.213,P=0.476	*(r)*0.145 ,P=0.522
SLEDAI(SLR)	*(r)*0.314 ,P=0.180	-
DAS28	-	(r)0.264, P=0.207
Larsen score	-	(r)0.065, P=0.735
ESR	*(r)*-0.068, P=0.842	(r)0.250 ,P=0.336
C-Reactive protein	*(r)*0.354 ,P=0.271	(r)0.299 ,P=0.233
Red blood cell count	*(r)*0.128 ,P=0.602	(r)0.105,P=0.602
White blood cell count	*(r)*0.050 ,P=0.815	(r)-0.317 ,P=0.128
Platelets count	(r)-0.491 ,P=0.022*	(r)-0.073 ,P=0.731
Triglyceride	*(r)*-0.074 ,P=0.753	(r)-0.180 ,P=0.387
Creatinine	*(r)*0.266,P=0.234	(r)0.426 ,P=0.065
Complement 3	*(r)*-00.207 ,P=0.438	-
Complement 4	*(r)*-0.147 ,P=0.538	-
Ds-DNA antibodies	*(r)*-0.148 ,P=0.503	-
ANA	*(r)*0.230 ,P=0.247	-
Anti- citrullinated protein antibody	-	(r)-0.201,P=0.350

• All clinical and laboratory parameters had insignificant correlations with serum resistin levels. Non-Significant (NS) (p > 0.05).

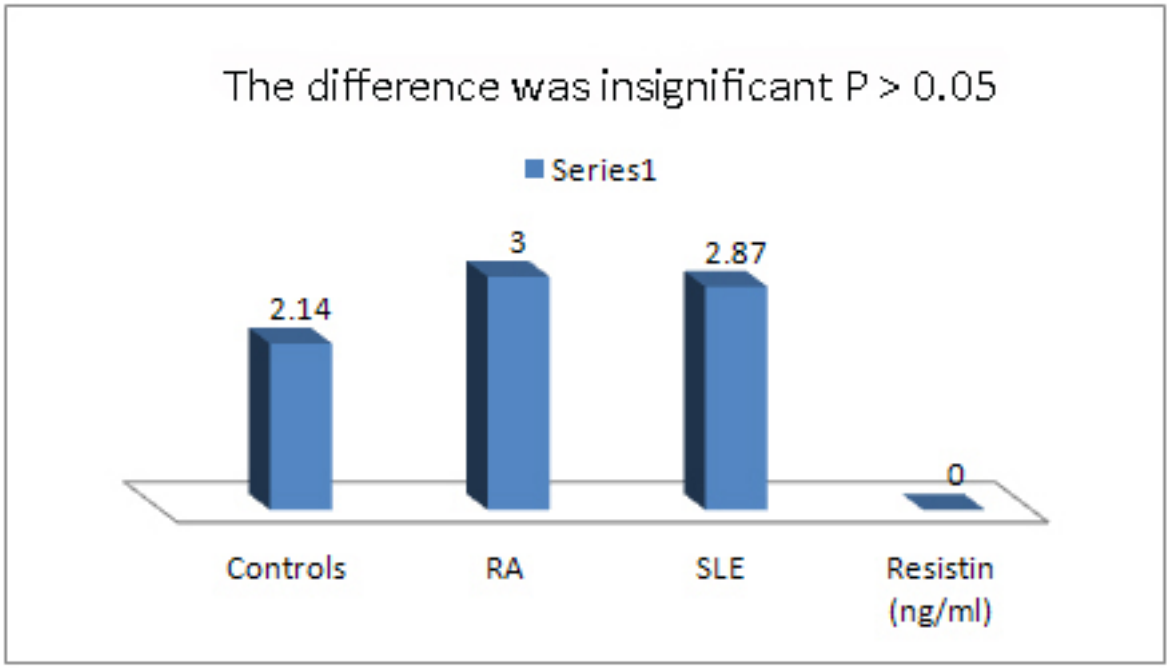
Table 3: Correlation of Serum Resistin levels in SLE, RA patients and control (ANOVA test)

Mean ±SD		SLE	RA	Controls	p value
Serum level,ng/ml	Resistin	2.86± 0.02	3.00±0.06	2.41 ±0.08	p1=0.233 p2=0.233 p3= 0.09

• Relation between two groups of SLE and RA patients and control group,

• p 1= between SLE patients and control, p 2= between RA patients and control, p 3= between SLE patients and RA. Non-Significant (NS) p > 0.05.

Figure 1: Mean of Serum Resistin Levels in SLE, RA and Control groups



Discussion

The immune system requires a proper energy balance for its physiological functions. In the past years, an important connection has been evidenced between that system and metabolism, with the identification of obesity as a predisposing factor for the development of several disorders, such as some immune-mediated diseases. The adipose tissue is not inert, and has been considered an organ with immune and neuroendocrine functions. That tissue produces several mediators, such as resistin, tumor necrosis factor alpha (TNF-a), interleukin 6 (IL-6), interleukin 1 (IL-1), chemokine ligand 2 (CCL2), plasminogen activator inhibitor type 1, and complement components, all participating in the innate immune response as pro-inflammatory mediators (16).

Macrophages are components of adipose tissue and actively participate in its activities. Furthermore, cross-talk between lymphocytes and adipocytes can lead to immune regulation. Adipose tissue produces and releases a variety of pro-inflammatory and anti-inflammatory factors, including resistin, the adipocytokines leptin, adiponectin, and visfatin, as well as cytokines and chemokines, such as TNF-a, IL-6, monocyte chemo-attractant protein-1, and others. Reduced leptin levels might predispose to increased susceptibility to infection caused by reduced T-cell responses in malnourished individuals (17).

Resistin, a novel adipocyte-secreted hormone, has gained attention for its involvement in insulin resistance in obesity and diabetes mellitus. Several groups have reported a close relationship between resistin and inflammation. Resistin increases the production of pro-inflammatory cytokines TNF-a and interleukin (IL)-12, both of which are important for T cell development (18).

In the current study, the mean serum level of resistin was highest in RA patients although there were insignificant differences of its level between SLE patients and controls (p=0.233), RA patients and controls (p=0.07) as well as SLE and RA patients (p=0.586). There is no agreement over the concentrations and function of resistin in SLE, because of a limited number of studies and their inconsistent results.

Data demonstrated by several authors were in agreement with our results. Almehed et al. found that serum resistin levels in controls were similar to those of SLE patients (1). Chung et al. have assessed the concentrations of resistin, visfatin, leptin

and adiponectin in 109 patients with SLE. They did not find statistically significant differences in resistin concentrations among SLE patients and control subjects (p=0.41) (19). Otero et al. (20) and Forsblad et al. (21) also found no difference in resistin concentration between RA patients and healthy controls. Yoshino et al. reported that there were no statistically significant differences in serum resistin levels between the RA patients (22).

Moreover, Yee et al. (23), Heilbronn et al. (24) and Iqbal et al. (25) showed no significant correlation between BMI and resistin levels in normal individuals. Senolt et al. (26) and Canruc et al. (27) found no significant correlation was found between BMI and serum resistin levels in RA patients. Bokarewa et al. did not find a relation between serum resistin levels and disease duration in RA patients. No significant correlations were found between serum resistin levels of SLE or RA patients and their disease duration (28). Bokarewa et al. found no significant difference of resistin levels between RA patients and healthy controls. Resistin levels in blood were neither related to the duration of RA, age of the patients, nor to circulating C-reactive protein levels or white blood cell counts (28).

In addition, Canruc et al. (27) and Kassem et al. (29) found no significant correlation was found between BMI and serum resistin levels in SLE or RA patients. Canruc et al. did not find a relation between serum resistin levels and disease duration in RA patients. They found no significant correlations between ESR or CRP and serum resistin levels in RA patients (27). Bokarewa et al. showed resistin levels in blood were not related to circulating C-reactive protein level in RA patients (28).

Bokarewa et al. (28), Canruc et al. (27) found no significant correlation between serum resistin levels and white blood cell count in RA patients. Elshishtawy et al. found insignificant correlation between serum resistin levels and SLEDAI ($p>0.05$) (30).

On the contrary, Elshishtawy et al. found a highly significant difference in the serum resistin levels of SLE patients compared to the control group ($p<0.0001$) (30). Migita K et al. (31) found serum resistin levels to be significantly higher in RA patients compared to the control subjects ($P= 0.0005$) (1). Also, Yoshino et al. (21) found significant correlation between serum levels of resistin and BMI (1). Zhang et al. (32) and Yannakoulia et al. (33) reported about correlation of resistin levels with BMI in normal individuals where resistin levels correlated significantly with adiposity in obese individuals.

In contrast to our result, Migita et al. (31), Senolt et al. (26) and Kassem et al. (29) found statistically significant correlations between resistin levels in the serum of RA patients and ESR and CRP. However, Senolt et al. (26) found a positive association between serum resistin level and disease duration in patients with RA (1). Gonzalez et al. found a highly significant association between the platelet count and resistin levels in RA patients (34). In our study, we find any significant negative correlation between serum resistin levels with the platelet count in SLE patients ($r = -0.491, p=0.022$), but Elshishtawy et al. had a statistically significant positive correlation between platelet count and serum resistin levels in SLE patients (30).

Almehed et al. found a relationship between serum resistin levels and the severity of inflammation, bone mass density (BMD) and renal function in SLE patients (1). They stated that the association between resistin, ESR, and complement 3 (C3) levels, observed in their study, may reflect disease activity (1).

However, Senolt et al. found a positive correlation between serum resistin levels and disease activity based on DAS 28 in patients with RA. Forsblad et al. (21), Kassem et al. (29) and Rho et al. (35) found a significant positive correlation between serum resistin levels and Larsen score for radiological joint damage in RA patients ($p< 0.05$). In one study, the authors found a relationship between serum resistin levels and the severity of inflammation and renal function in SLE patients (1).

In our study, explanation of serum resistin levels did not correlate with clinical or laboratory markers except platelet counts; it could be due to difference in disease activities, age, BMI, disease duration in SLE and RA patients. Also, this can be explained by the fact that serum resistin may not have a main role in the pathogenesis of these diseases, but other mediators may have a main role in the pathogenesis of SLE and or RA patients.

Conclusion

We conclude that serum resistin levels did not correlate with clinical or laboratory markers except platelet counts in SLE and or RA cases, although it has a higher level in these diseases compared to the controls. In explanation of our results, it could be difference in disease activities, age, BMI or disease duration in SLE and RA patients. Moreover, resistin may not have a main role in the pathogenesis of SLE and or RA patients. We recommended that further longitudinal studies including a greater number of patients are required and further comparative studies are required.

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