Research Article

Resistin as an inflammatory marker in Lupus Nephritis

Faten I. Mohamed*, Shimaa S. Ahmed*, Moustafa A. Abu El-Ella and Maha A. Ali***
* Department of Rheumatology and Rehabilitation, Faculty of Medicine, El-Minia University,
** Department of Clinical Pathology, Faculty of Medicine, El-Minia University, Egypt.

Abstract
Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominately affects women. It is characterized by a broad spectrum of clinical manifestations. Adipokines are a diverse family of soluble mediators with a range of specific actions on the immune response. Among the various adipokines is Resistin. **Methods:** 26 patients with lupus nephritis with age ranged between 18-48 years and 20 healthy age, sex and BMI matched individuals were enrolled in this study. Full history, clinical examination and laboratory investigations were performed for all patients including serum resistin level. **Results:** The level of serum resistin was higher in the patients than the controls ($p < 0.001$). Also, Serum resistin level correlated positively with the levels of ESR ($p< 0.001$), CRP ($p= 0.008$). Serum resistin levels correlated negatively with levels of C3 ($p< 0.001$) and C4 ($p< 0.001$). **Conclusion:** Serum resisitin level can be used as a marker of inflammation in patients with lupus nephritis.
Keywords: Systemic lupus erythematosus, lupus nephritis, adipokines, resistin.

Introduction
Systemic lupus erythematosus (SLE) is a chronic multi-systemic autoimmune disease with a highly heterogeneous pattern of clinical and serological manifestations. Its course differs in different individuals and is unpredictable within the same patient over time, which makes it interesting and challenging to manage. The pathogenesis of SLE is the result of interactions between genes, hormones and the environment, but its precise etiology is mostly unknown[(1)].

Among the various clinical manifestations of SLE, renal involvement is one of the most important causes of morbidity and mortality[(2)]. Renal involvement occurs in 30-50% of patients with SLE, usually early in the disease course[(1)].

Adipose tissue synthesizes and releases physiologically active molecules that are known as adipokines or adipocytokines, including resistin, leptin, and adiponectin, as well as IL-1, IL-6, IL-10, and tumor necrosis factor (TNF)-α[(3)]. Adipokines not just act like hormones in glucose homeostasis and appetite regulation, but more than like cytokines, thus playing a key role in inflammation and immunomodulation[(4)].

Adipokines have recently been implicated as mediators of immune and inflammatory processes. Systemic autoimmune diseases are associated with chronic intractable inflammation. Although the etiology of these diseases is still unknown, investigations into their pathogenesis have confirmed the involvement of various proinflammatory cytokines. Some studies have suggested that adipokines may also play a role in the pathogenesis or inflammatory processes of systemic autoimmune diseases[(3)].

Resistin is a recently described, low-molecular-weight, cystein-rich secretory peptide[(5)]. It is also known as adipocyte-specific secretory factor. Animal studies show that resistin is produced mainly in white adipose tissue and may be the linkage between obesity and insulin resistance. In humans, the role of resistin is not yet fully established[(6)].

There is evidence that resistin has pro-inflammatory properties and is abundant in inflammatory diseases (for instance, rheumatoid arthritis (RA)[(7)] and Crohn's disease[(8)]) and also is associated with inflammatory markers in several different populations[(9)]. In humans, resistin is expressed in inflammatory cells,

leukocytes, and macrophages[10] and has the potency of inducing production of interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α)[11].

Aim of the work

The aim of this study was to assess the serum levels of resistin in patients with lupus nephritis and to evaluate its role as a marker of inflammation.

Patients and methods

Twenty-six patients (25 females and 1 male) who fulfilled the Systemic Lupus International Collaborating Clinics classification criteria (SLICC 2012)[12] and had biopsy proven lupus nephritis were involved in this study. The mean age was 28.35 ± 7.11 years (range from 18-48 years) and the mean ± SD disease duration was 46.88 ± 43.01 months. Twenty healthy age, sex and BMI matched individuals were served as a control group. Excluded from this study are patients with Juvenile SLE, hepatitis, Diabetes Mellitus, hypertension, morbid obesity, malignancies, infectious diseases, liver diseases, inflammatory bowel diseases, other autoimmune diseases, end-stage renal disease, patients with angina, myocardial infarction or stroke and pregnant patients. The nature of the study was explained to all patients. The laboratory procedures represent standard care and pose no ethical conflicts. A consent was obtained from all patients.

All patients were subjected to detailed medical history and complete physical examination. Laboratory investigations were performed for all patients including complete blood count (CBC), Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid Factor (RF), renal Function tests, simple urine analysis, 24- hour urine protein, urine protein/creatinine ratio, serum total cholesterol and triglycerides, Serum anti-nuclear antibody (ANA) and anti-double stranded DNA (anti dsDNA) levels, serum complement 3 and complement 4 (C3, C4) levels and serum Resistin level. Renal biopsy was done for all patients. Disease activity was assessd using SLE disease activity index (SLEDAI-2K).

Statistical analysis

Analysis of data was done by personal computer using SPSS (Statistical program for social science) version 19. The data of all software patients and controls were fed into an IBM personal computer. Data were expressed as mean ± SD for parametric variables and as number and percent for non-parametric variable. Comparison between groups for parametric data was done by independent samples t-test (unpaired t-test). Chi – square (X2) test was used to compare qualitative variables. The difference was expressed as probability of value (P value). The difference was considered significant if $P < 0.05$. Pearson and Spearman correlation coefficients (r) were calculated for detection of parametric and non-parametric correlations respectively.

Results

Demographic data of the studied patients:

This study included 26 SLE patients. 20 healthy age, sex and BMI matched individuals were served as a control group. Their age ranged from (18-48) years with a mean± SD of 28.35 ± 7.11 years. SLE disease duration ranged from (5-180) months, with a mean± SD of 64.88 ± 43.01 months.

Demographic characteristics of all the studied SLE patients are shown in (Table 1).

Clinical characteristics of SLE patients:

Clinical Characteristics of SLE patients are shown in (Table 2) Malar rash was found in 23 patients (88.5%) and photosensitivity was in 21 of them (80.8%). Alopecia was found in 19 patients (73.7%), oral ulcers were in 18 patients (69.2%) and 20 patients (76.9%) had fever. Twenty patients had myalgia (76.9%). Arthralgia occurred in 22 patients (84.6%) and arthritis was in 15 patients (57.7%). The patients' BMI ranged from (20.80-39.20) kg/m2 with a mean of 27.54 ± 5.18. (Table 2).

Laboratory data for the studied SLE patients:

Regarding the laboratory findings in SLE patients, ESR level ranged from (15-120) mm with a mean ± SD of 57.38 ± 30.61 and CRP was positive in 10 patients (38.5%). Complement 3 (C3) ranged from 27.37-167 mg/dl with mean ± SD of 109.88 ± 44.34, and complement 4 (C4) ranged from 3.07-27.54 mg/dl with a mean ± SD of 15.19 ± 7.64. (Table 3).

Assessment of serum Resistin levels:

Serum resistin was measured for both patients and controls. The level of serum resistin of the

patients has ranged from (1.1-8.2) ng/ml with mean± SD of 3.24 ± 2.32 and for the control group (Group 2), the serum resistin ranged from (0.50-2) ng/ml with a mean± SD of 0.89 ± 0.34. A comparison of serum Resistin between patients and controls showed a high significant difference between the patients and the controls *(P< 0.001)* (Table 4).

Correlation of the serum Resistin level with inflammatory markers of studied patients: Among patients with SLE, the serum resistin level correlated positively with the levels of ESR *(p< 0.001)* and CRP *(p= 0.008).* A negative correlation was found between serum resistin level the levels of C3 *(p< 0.001)* and C4 *(p< **0**.001)* (Table 5).

Table 1: Demographic characteristics and disease duration of studied lupus nephritis patients:

	Lupus Nephritis (n = 26)
Age (years)	
Range	18-48
Mean ± SD	28.35 ±7 .11
Sex	
Male; No. (%)	1 (3.8)
Female; No. (%)	25 (96.2)
SLE disease duration (months)	
Range	5-180
Mean ± SD	46.88 ± 43.01

Table 2: Clinical characteristics of studied lupus nephritis patients:

Clinical Characteristic		**No (%)**
Malar rash		23 (88.5)
Photosensitivity		21 (80.8)
Oral ulcers		18 (69.2)
Alopecia		19 (73.7)
Fever		20 (76.9)
Arthralgia		22 (84.6)
Arthritis		15 (57.7)
Myalgia		20 (76.9)
BMI *(kg/m2)*	**Range**	20.80- 39.20
	Mean ± SD	27.54 ± 5.18

Table 3: Laboratory Investigations for the studied lupus nephritis patients:

Laboratory investigations	
ESR *(mm)*	
Range	15-120
Mean ± SD	57.38 ± 30.61
C3 *(mg/dl)*	
Range	27.37-167
Mean ± SD	109.88 ± 44.34
C4 *(mg/dl)*	
Range	3.07-27.54
Mean ± SD	15.19 ± 7.64
C-Reactive Protein (CRP)	
Positive (%)	10 (38.5)

Table 4: Comparison of serum Resistin levels between patients and Controls:

	Group 1 (patients) (n = 26)	**Group 2 (Control) (n = 20)**	**t**	**P- value¥**
Serum Resistin *(ng/ml)*				
Range	1.1-8.2	0.5-2	4.44	*<0.001****
Mean ± SD	3.24 ± 2.32	0.89 ± 0.34		

By Independent sample T-test

Table 5: Correlation of serum Resistin level with laboratory investigations of the studied patients:

		Serum Resistin
ESR	**r**	0.83
	p	*<0.001****
CRP	**r**	0.51
	p	*0.008***
C 3	**r**	-0.87
	p	*<0.001****
C 4	**r**	-0.81
	p	*<0.001****

By Pearson and Spearman correlation

Discussion

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with multi-organ inflammation characterized by a variety of clinical manifestations [13].

Adipose tissue has become a subject of intensive research for its ability to secrete numerous hormones and cytokines called adipokines with important systemic metabolic effects. One of these adipokines is resistin [14].

In our study, we found that serum resistin levels were elevated in all our patients compared to the healthy controls *($p < 0.001$)*. These findings came in accordance with other investigators. A study performed by Liu et al., (2009) [15]. Also, Baker et al., (2011)[16] and Elshishtawy et al., (2012)[17] found significant differences in mean resistin levels between the SLE patients and controls.

Supporting our results regarding the role of resistin in inflammation and the correlation we found in our study between serum resistin and each of ESR and CRP, Almehed et al., (2008) stated that markers of inflammation in SLE such as raised ESR, CRP, immunoglobulin G (IgG), proinflammatory cytokines, and low serum albumin levels correlated positively with resistin in serum. Also, in agreement with our findings, Baker et al., (2011)[16]; Elshishtawy et al., (2012)[17] and Rezaieyazdi et al., (2017)[18] all concluded that resistin levels correlated positively with ESR and CRP levels. However, Chung et al., (2009)[19] found a relatively weak association between resistin and ESR but no association with CRP.

In conclusion, this study suggests that serum resistin level can be used as a marker of inflammation in lupus nephritis patients.

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