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Serum Adiponectin Level in Patients with Systemic Lupus Erythematosus and its Correlation with Disease Activity

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ABSTRACT

Background: *Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disorder characterised by widespread inflammation of connective tissues affecting the skin, joints, kidneys, heart, lungs, and nervous system. SLE is associated with significant morbidity, thus requiring prompt evaluation, appropriate therapy and long-term follow-up.*

Objective: *This study was performed to measure serum adiponectin in SLE patients and to correlate it with SLEDAI and to evaluate its role as a biomarker of activity in SLE patients specially renal in the hope of preventing or at least postponing renal damage.*

Patients and methods: *This study included 72 subjects, 36 patients and 36 volunteers. The patients were divided into three groups. Group I (active renal) 12 patients having renal disease activity, group II (active non-renal) 12 patients having non-renal disease activity and group III (inactive SLE). 36 apparently healthy volunteers were included (group IV) as a control group.*

Results: *A highly significant difference in serum adiponectin between SLE groups and control group. A highly significant positive correlation between serum adiponectin and 24 h protein in urine. Negative correlation between serum adiponectin and C3 & C4. A significant difference between SLE groups as regards serum anti-double stranded DNA titres, which were higher in renal group patients, also C3 & C4 levels which were lower in the renal group. Serum adiponectin level was not correlated with SLE Disease Activity Index (DAI).*

Conclusion: *Adiponectin level was strongly associated with active SLE with renal disease. Adiponectin level in SLE patients was not correlated with SLEDAI. It may be a promising biomarker for prediction of renal activity of SLE.*

Keywords: *Adiponectin Level, SLE, SLEDAI.*

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I. INTRODUCTION

The laboratory tools used to measure kidney damage are crude and relatively imprecise in their ability to indicate a flare of lupus nephritis. Proteinuria, hematuria, pyuria, presence of urinary casts and serum creatinine levels are all non-specific renal markers. They may correlate with kidney damage, but they unfortunately cannot predict a renal flare [(1)].

Adipose tissues form an endocrine organ that regulates immune processes and inflammation by secreting bioactive mediators called adipokines. Adipokines, including adiponectin, visfatin, leptin and ghrelin[(2)].

Adiponectin is a 30-kDa plasma protein produced mainly by adipocytes macrophages. It is structurally similar to complement component C1q and function as an anti-inflammatory and pro-inflammatory factor [(3)]. Adiponectin inhibits pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 and adhesion molecules. Also, it is involved in the modulation of inflammatory responses. Adiponectin also has pro-inflammatory effects on various cells in the immune system. Adiponectin can increase the production of IL-6 and metalloproteinases (MMPs) from endothelial cells and monocytic cells. Adiponectin may play a role as an enhancer of the inflammatory response in the process of immune response and inflammation [(4)].

The anti-inflammatory properties of adiponectin may be a major component of its beneficial effects on metabolic disorders including systemic lupus erythematosus. Higher circulating adiponectin levels in SLE patients may positively correlate with inflammatory markers[(3)]. High levels of adiponectin have been found in patients with SLE in comparison with healthy controls. Some studies reported that plasma adiponectin levels are increased in patients with renal SLE compared to healthy controls and patients with non-renal SLE [(5)].

II. AIM OF THE WORK

This study aimed to measure serum adiponectin in SLE patients and to correlate it with SLEDAI and to evaluate its role as a biomarker of activity in SLE patients specially those having renal affection in the hope of preventing or at least postponing renal damage.

Ethical approval and patient consent:

This study was carried out after review and approval by the institutional review board committee. A signed consent was taken from all subjects for ethical consideration.

III. SUBJECTS AND METHODS

This study was carried out over 8 months on the outpatients & inpatients of Internal Medicine Department and Rheumatology Department at Faculty of Medicine, Zagazig University Hospitals & Armed Forces Hospital in Alexandria on 72 subjects. They were divided into 4 groups;

1- GROUP I (active renal group): patients having SLE with renal disease activity,they were 10 females (83.3%) and 2 males (16.7%), their ages ranged from 21– 44 years with a mean value of 34.0 ± 7.92.

2- GROUP II(Active Non renal group): It included 12 SLE patients, all were 11 females (91.65%) and one male (8.35%). Their ages ranged from 23-45 years with a mean value of 35.08 ± 8.31 years. These patients had no renal disease (SLEDAI score > 6).

3- GROUP III (Inactive SLE group): It included 12 SLE patients, all were10 females (83.3%) and 2 males (16.7%). Their ages ranged from 24-48 years with a mean value of 34.08±8.44 years. These patients had inactive SLE (SLEDAI score < 6).

4- GROUP IV (Control group): It included 36 apparently healthy volunteers. Their age and sex were matched with the patients. They were 30 females (83.3%) and 6 males (16.7%). Their ages ranged from 19 – 54 years with a mean value of 33.5 ± 8.59 years. Clinical examination as well as routine laboratory investigations confirmed their healthy state.

Exclusion criteria: Patients with diabetes mellitus, malignancies, metabolic disorders, pregnancy and patients undergoing hemodialysis or with a history of renal transplantation were also excluded.

All patients were subjected to the following:

1. Full history taking: With special stress on the following; onset, course and duration of the disease, constitutional manifestations (fever, malaise and weight loss), joint pain and swelling, morning stiffness, falling of hair,photosensitivity & skin rash,oral or nasal ulcers, Raynaud's phenomenon,subcutaneous nodules, lymph node enlargement, dryness of eyes and/or mouth, vasculitic lesions, other system affection and previous medications.

2. General Examination: General appearance, blood pressure, pulse and temperature, lymph node examination and lower limb oedema. Skin examination for rash, oral ulcers and subcutaneous nodules. Hair examination for alopecia and lupus hairs. Cardiac examination for pericardial rub (effusion). Chest examination for crepitations and pleural rub (effusion). Full neurological examination. Abdominal examination for hepatosplenomegally& tender renalangle.

3. Local examination of locomotor system: (a) Inspection of Joint swelling, muscle wasting and deformities. (b) Palpation for hotness, tenderness & synovial thickening. Swelling of bone, soft tissue or effusion and crepitations. (c) Range of motion (active and passive). (d) Special tests for knee effusion (bulge sign, pateller tap and cross fluctuation).

4. Investigations: Complete blood picture, erythrocyte sedimentation rate,C- reactive protein,complete urine analysis and 24 hr urinary protein. Kidney function tests (blood urea & creatinine). Serum complement C3 by use of immunodiffusion plate. Complement 4 by use of immunodiffusion plate. ANA done by ELISA. Anti-dsDNAtitre done by latex agglutination test for the detection of anti-DNA in human sera. Serum Adiponectin measurements by enzyme-linked immunosorbent assay (ELISA).

5- Assessment of disease activity: The disease activity was assessed according to the SLEDAI **[(6)].** SLEDAI was classified according to **Esdaile *et al.*[(7)]**into: Inactive disease: if SLEDAI < 6 points and active disease: if SLEDAI ≥ 6 points.

The presence of renal disease was defined as a renal SLEDAI score of > 4, corresponding to the presence of any one of the following on urine analysis: haematuria, proteinuria, pyuria or urinary red cell casts. Thus, scores for the renal SLEDAI can range from 0 (no renal disease activity) to a maximum of 16 **[(8)].**

In our study, all SLE patients were followed up through:

- Collection of clinical data included in SLEDAI scores for each subject.
- Collection of blood samples for measurement of serum adiponectin.
- 24 hour urine collection was taken for total urine protein. Also, standard urine analysis and urine protein/creatinine ratio were done.
- Blood samples were obtained for complete blood count, serum C3 and C4, and anti-double-stranded (ds) DNA antibody titres.
- SLEDAI scores (The renal SLEDAI, The global SLEDAI and the non-renal SLEDAI) were calculated.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following: P-value ≤ 0.05 was considered significant. P-value < 0.001 was considered as highly significant. P-value > 0.05 was considered insignificant.

IV. RESULTS

This study comprised 72 subjects. Group 1: Active renal group included 12 patients having renal disease activity.They were 10 females (83.3%) and 2 males (16.7%), their ages ranged from 21– 44 years with a mean value of 34.0 ± 7.92 years.

Group II: Active non- renal group included 12 patients having non-renal disease activity. They were 11 females (91.65%) and 1 male (8.35%), their ages ranged from 23 – 45 years with a mean value of 35.08 ± 8.31 years.

Group III: Inactive SLE. They were 10 females (83.3%) and 2 males (16.7%), their ages ranged from 24-48 with a mean value of 34.08 ± 8.44 years. Group IV (control group) included 36 persons apparently free from any relevant disease, age and sex matched with patients. They were 30 females (83.3%) and 6 males (16.7%), their ages ranged from (19-54) years with a mean value of 33.5 ± 8.59 years.

Table (1): Age, BMI and sex distribution between cases and control

	Case	**Control**	**t/X^2**	**P**
Age	34.38 ± 8.0	33.5 ± 8.59	0.454	0.651
BMI	22.28 ± 1.57	22.24 ± 1.75	0.092	0.927

Sex	**Female**	**N**	31	30		
		%	86.1%	83.3%		
	Male	**N**	5	6	0.11	0.74
		%	13.9%	16.7%		
Total		**N**	36	36		
		%	100.0%	100.0%		

Age was distributed as 34.38 ± 8.0 and 33.5 ± 8.59 respectively between cases and control with no significant difference between them. Also, there was no significant difference regarding BMI or sex distribution (Table 1).

Table (2): Lab distribution between cases and control

	Case	**Control**	**T**	**P**
Hb (g/dl)	10.68 ± 1.4	13.06 ± 1.13	3.246	0.03*
Platelet (mcL)	266.61 ± 7.01	276.44 ± 7.98	-0.556	0.580
WBCs (mcL)	6.5 ± 1.1	6.23 ± 1.6	0.565	0.574
Urea(mg/dl)	30.66 ± 6.35	26.97 ± 7.83	2.197	0.031
Creatinine (mg/dL)	1.1 ± 0.25	0.83 ± 0.11	1.110	0.045

From table (2), it was observed that there was significant difference between cases and control groups as regards Hb. There were non-significant differences as regardsWBCs andplatelet counts. Creatinine was higher in cases than control group.

Table (3): Inflammatory markers distribution between cases and control

	Case	**Control**	**T**	**P**
Anti-ds DNA	386.47 ± 124.6	68.72 ± 19.55	6.548	0.001**
ESR	45.72 ± 15.1	37.72 ± 10.08	1.879	0.057
CRP	12.88 ± 3.01	7.21 ± 2.28	2.727	0.008*
C3	68.02 ± 22.4	106.69 ± 23.13	-5.594	0.001**
C4	23.83 ± 7.57	33.0 ± 9.32	-2.886	0.005*

Anti-ds DNA, CRP were significantly higher among cases. C3 and C4 were significantly lower among SLE group (Table 3).

Table (4): Serum adiponectin distribution between cases and control

	Case	Control	Mann Whitney	P
Serum adiponectin	1.05	0.53	4.660	0.001**

From this table it was observed that, there was ahighlysignificant difference in the level of serum Adiponectin between SLE groupsand the control group(Table 4).

Table (5): Inflammatory markers distribution between cases and control

	Group I	Group II	Group III	F	P
Anti-dsDNA	369.16 ± 128.6	488.16 ± 164.5	198.08 ± 65.5	6.058	0.006*
ESR	55.0 ± 18.6	36.41 ± 13.54	33.75 ± 11.32	2.429	0.104
CRP	13.6 ± 3.8	12.5 ± 2.21	11.58 ± 3.21	2.086	0.140
C3	47.0 ± 16.8*	77.91 ± 25.1	81.16 ± 25.3	4.021	0.027*
C4	11.93 ± 2.54*	29.51 ± 16.2	34.06 ± 10.7	15.647	0.001**

Table (5) showed that Anti-dsDNA was significantly different among groups as it was significantly higher in group II followed by group I then finally group III, C3 and C4 were significantly lower among group I.

Table (6): 24 H protein in urine distribution among SLE groups

	Group I	Group II	Group III	Kruskalwalis	P
24 H ptn in urine	3550 *	277.5	107.5	73.196	0.001**

From the table (6), it was noticed thattherewerehighly significant differences (p 0.00)between SLE groups as regards 24 h ptn in urine. It was significantly higher in group I (active renal group).

Figure (1): ROC Curve for Lupus with renal cutoff Sig AUC with cutoff >2.9 and sensitivity 92.5% and specificity 98.3% (Figure 1).

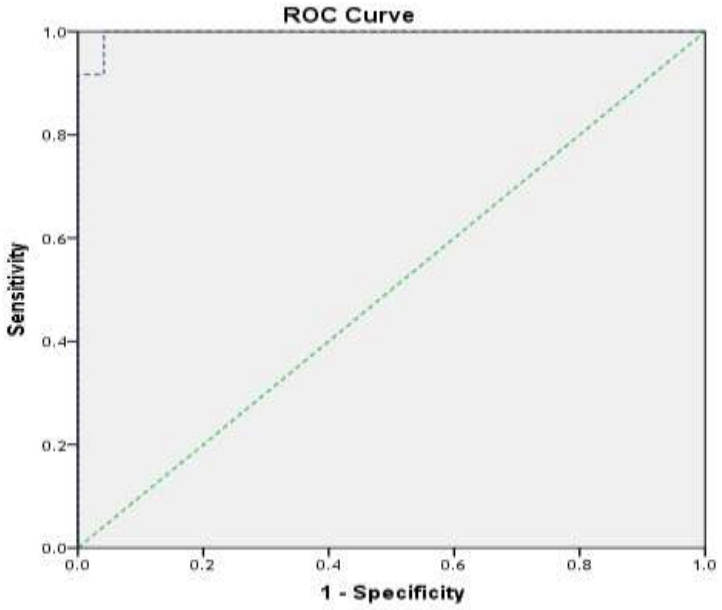

Table (7): SLEDAI distribution between group I and group II

Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.997	>2.9	0.00**	.985	1.000	92.5%	98.3%

	Group I	Group II	T	P
SLEDAI	9.75 ± 3.3	9.41 ± 3.39	0.22	0.82

No significant difference between group I & group II (Table 7).

Table (8): Correlation between adiponectin and other parameters

		Serum adiponectin
Age	R	-.048-
	P	.686
BMI	R	-.011-

	P	.929
ESR	R	.192
	P	.107
CRP	R	.110
	P	.358
Platelet	R	-.154-
	P	.197
C3	R	-.318-**
	P	.006
C4	R	-.406-**
	P	.000
24H ptn in urine	R	.838**
	P	.000

There were significant negative correlation between adiponectin and C3 & C4. Also, there was significant positive correlation between adiponectin and 24H ptn in urine (Table 8).

V. DISCUSSION

In our study, age was distributed as 34.38 ± 8.0 and 33.5 ± 8.59 between cases and control respectively with no significant difference between them and also we didn't find significant difference regarding BMI or sex distribution. Similar to **Marjon*et al.*[9] and Elbedewy*et al.*[10]**study which didn't find significant difference regard Age, BMI or sex distribution.However,in contrast with**Guebre-Egziabher*et al.*[11]** study, which found positive correlation between BMI and adiponectin. In our study we did not find a statistical correlation between adiponectin and BMI perhaps because our patients were selected in normal range of BMI.

Our study results found significant difference between cases and control group as regards Hb. Decreased Hb in cases may result from several mechanisms and more than one may be operating at any time. Anemia of chronic disease is the most common, but a low hemoglobin can be caused by auto-antibodies to red cells as part of the auto-immunity, or it may be the result of impaired erythropoietin production by kidneys involved in the SLE, gastrointestinal blood loss from anti-inflammatory therapy, increased red cell destruction from hypersplenism or a drug-induced immune phenomenon.

In sub groups of SLE, there was decrease of Hb in group I and group II but insignificant. This is similar to **Elbedewy*et al.*[(10)]**study in which Hb, WBCs, lymphocytes andplatelet counts had no significant differences among groups.

Our study revealed that, there was no correlation between Hb, WBCs, platelets and serum adiponectin. Our study is compatible with **Elbedewy*et al.*[(10)] and Zoccali *et al.*[(12)]** regarding creatinine and urea as there was no correlation between serum adiponectin and urea & creatinine.

In our study, anti-ds DNA, CRP were significantly higher among cases of our study patients. In sub group analysis, anti-ds DNA was significantly different among groups as it was significantly higher in group II followed by group I then finally group III. C3 and C4 were significantly lower among group I. This is in agreement with **Elbedewy*et al.*[(10)]**study, in which anti-ds DNA, CRP were significantly higher among SLE patients with lupus nephritis (LN) versus without LN ($p < 0.001$) and between active SLE and inactive SLE patients ($p < 0.001$). C3 and C4 were significantly lower in group I.

In our study, we observed that there was ahighlysignificant difference in the level of serum adiponectin among SLE groups(1.05) and the control group (0.53)(P=0.00).In subgroup analysis of our study patients, there was significant difference in the level of serum adiponectin betweenSLE groups. Group I was significantly higher regarding serum adiponectin level (P=0.001). This is in agreement with **Sada*et al.*[(5)]** study, **Chung *et al.*[(13)]** study, **De Sanctis*et al.*[(14)]** study &**Reynolds *et al.*[(15)]**study. They measured the concentrations of different adipocytokines as adiponectin in patients with SLE and control subjects. They recorded that serum adiponectin was higher in patients with SLE than in controls. They all concluded that adiponectin is involved in the inflammation in SLE. Also **Toussirot*et al.*[(16)]** study documented that adiponectin levels were higher in patients with systemic autoimmune disease including SLE than in control subjects.

A meta-analysis published in 2017 found that patients with SLE had significantly higher serum adiponectin levels compared to control subjects. Adiponectin is considered primarily to act as an anti-inflammatory molecule in most inflammatory diseases including SLE **[(17)].** Interestingly, **Reynold *et al.*[(15)]** hypothesized that increased adiponectin concentration in SLE patients could represent a compensatory response of organism against inflammation. However, some researchers find this explanation unconvincing and point to the role of adiponectin in nuclear factor κB activation **[(18)].**

In our study, ROC curve for Lupus with renal cutoff >2.9 had sensitivity of 92.5% and specificity of 98.3%. So, Serum adiponectin could be considered as a promising biomarker for perdiction of SLE activity with renal involvement due to its high sensitivity and specificity.

In our study, there was significant positive correlation between serum adiponectin and 24 hours protein in urine. This is in agreement with **Diaz-Rizo*et al.*[(19)]** who reported that higher serum adiponectin levels were associated with proteinuria in LN patients. Adiponectin levels correlated significantly with the severity of proteinuria of 24 h. Increase in adiponectin levels remains associated with the intensity of proteinuria. Also, **Zoccali *et al.*[(12)]** study stated that 24- hour proteinuria was strongly correlated with serum adiponectin.

Our study results found that the most predominant manifestation comparing clinical data in both groups was photosensitivity (50% in thenon-renalgroup &58.3% in the renal group) followed by fever and arthiritis. There was non-significant differences between non-renal and renal groups as regards all the clinical manifestations except for fever that was associated with group I**.** This is similar to **Mohammed *et al.*[(20)]**study where disease activity

was assessed using the SLE disease activity index (SLEDAI). Comparison between the two groups showed non-significant statistical differences between SLE patients with and without different clinical manifestations (fever, fatigue, vasculitic rash, photosensitivity,arthralgia,arthritis,neuropsychiatric and renal manifestations).

In our study, there was no statistical correlation between groups regarding SLEDAI. This similar to **Dini *et al.*[17]** who found no correlation between adiponectin concentrations and SLEDAI scores among SLE patients. Although serum adiponectin levels were higher in SLE patients, they did not appear to be associated with disease activity. On the contrary, **Vadacca*et al.*[21]** observed a correlation between adiponectin levels and activity index score in SLE. Absence of association could be explained by the fact that SLEDAI constitutes a clinical data for disease activity, which does not necessarily reflect changes in the levels of cytokines or hormones that influence inflammation.

In our study, as shown in table (8), there were significant negative correlations between adiponectin and C3 & C4 and this goes in agreement with **Elbedewy*et al.*[10]** study in which serum adiponectin had a highly significant inverse correlation with C3, and C4.

Our results stated that there were no significant correlations between serum adiponectin and ESR or CRP and this is in agreement with **Rovin*et al.*[22]** study. But our finding is in contrast with**Toussirot*et al.*[16]** study who stated that ESR and adiponectin were found to be markedly negatively correlated.

A major strength of our study is the adequate sample size among patients with SLE. Performing a subgroup analyses to better understand the effect of age, BMI, and region on serum adiponectin levels. However, our study faced some limitations:

(1)All SLE patients expressed diverse clinical manifestations, and disease activity of SLE patients were uniformly assessed by SLEDAI. This might complicate the statistical analysis.

(2) We used the commonly used SLEDAI scoring system to assess the disease activity of the SLE patients.

(3) Patients with SLE were currently receiving treatment with corticosteroids and high doses of these drugs may increase the serum levels of these adipokines.

(4) We could not perform renal biopsies for diagnosis and histological classification of LN in renal group patients.

VI. CONCLUSION

The Patients with SLE had higher serum adiponectin level compared to control subjects. Adiponectin level was strongly associated with active SlE with renal disease. Adiponectin level in SLE patients was not correlated with SLEDAI. It may be a promising biomarker for prediction of renal activity of SLE.

RECOMMENDATIONS

1) Early prediction of activity of SLE with renal involvement via assessment of serum adiponectin level.

2) Further evaluation of serum adiponectin as a marker of SLE activity specially kidney involvement in larger groups of SLE patients in larger prospective studies.

3) Confirmation of the fact that serum adiponectin links to renal disease activity by histopathologic findings by using renal biopsy.

4) To compare serum adiponectin with other biomarkers to find out which is most valuable and reliable as a marker of kidney involvement in SLE and whether these biomarkers contribute in disease pathogenesis.

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