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High serum leptin and adiponectin levels as biomarkers of disease progression in Egyptian patients with active systemic lupus erythematosus

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Abstract

Objectives: Leptin and adiponectin are adipose-derived immune modulators (adipokines) that may contribute to SLE pathology and symptoms. This study aimed to evaluate the associations of serum adiponectin and leptin with clinical manifestations and disease activity in SLE patients. **Methods:** This is a case control study, where 70 SLE patients and 50 age- and sex-matched healthy controls were enrolled from the Rheumatology and Rehabilitation Department of Beni-Suef University Hospital from June 2020 till April 2022. The SLE disease activity index (SLEDAI) and Systemic Lupus International Collaborative clinics/America Collage of Rheumatology damage index were used to assess disease severity. Laboratory parameters including erythrocyte sedimentation rate (ESR) and serum concentrations of antinuclear antibody (ANA), anti-double stranded DNA, complement 3 and 4, lipids, and C-reactive protein (CRP) were measured and compared between SLE and control groups. Serum adiponectin and leptin were also measured by enzyme-linked immunosorbent assays (ELISA). **Results:** Compared to healthy controls, SLE patients exhibited significantly greater serum leptin (21.1 vs 3.9 ng/mL, $p < 0.001$) and adiponectin (18.1 vs 4.8 ng/mL, $p < 0.001$), and both values were positively correlated with SLEDAI scores ($p = 0.048$ and 0.042). Higher serum leptin was significantly associated with lupus nephritis (LN) ($p = 0.048$) as well as greater body mass index ($p = 0.010$), ESR ($p = 0.002$), serum CRP ($p = 0.003$), total cholesterol ($p = 0.013$), and uric acid ($p = 0.002$), while higher adiponectin was significantly associated with LN ($p = 0.046$). **Conclusion:** Serum leptin and adiponectin levels are associated with the clinical and pathological manifestations of SLE, suggesting direct involvement in disease progression and utility as diagnostic biomarkers and therapeutic targets.

Keywords

Systemic lupus erythematosus, leptin, adiponectin, systemic lupus erythematosus disease activity index score

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organs, and clinical management is challenging due to symptom heterogeneity, unpredictable course, and recurrent flares.[1] Various organs and organ systems may be differentially affected by SLE,

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with each exhibiting periods of quiescence and disease activity, compounding the clinical heterogeneity. Moreover, SLE may ultimately cause irreversible organ damage. Environmental triggers, genetic susceptibility, microbial infection, cardiovascular disorders, hormonal imbalances, and metabolic disturbances are some of the potential predisposing factors for disease onset.[1]

Inflammatory responses in SLE are characterized by imbalances between pro- and anti-inflammatory cytokines. Therefore, it is critical to understand the contributions of pro- and anti-inflammatory signaling factors in SLE onset, progression, and recurrence. Indeed, the recent rise in patient survival is primarily due to improved treatments based on a greater understanding of immune dysregulation in disease pathophysiology.[2] Signaling factors regulating both systemic immune responses and metabolism may be particularly important in SLE pathogenesis and promising targets for therapeutic intervention.[2]

Human leptin is a non-glycosylated 167-amino acid peptide that acts as a cytokine-like immune modulator. It is largely produced in adipocytes of white adipose tissue, with lesser quantities produced by the stomach, musculoskeletal system, placenta, and bone marrow.[3] Leptin is a possible therapeutic target for autoimmune illness because it affects how the immune system responds to inflammatory signals. Patients with SLE usually demonstrate elevated serum leptin, especially patients with associated nephritis (lupus nephritis or LN).[4]

In addition, adiponectin is a 244-amino acid protein produced mainly by adipose macrophages implicated in SLE.[5] Adiponectin is classified as an adipokine, a group of cytokines, peptide hormones, and enzymes implicated in a wide range of biological activities including inflammatory and immunological processes.[6] Adiponectin function as an anti-inflammatory and pro-inflammatory factor, by inhibiting pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 and adhesion molecules or increasing the production of IL-6 and metalloproteinases (MMPs) from endothelial cells and monocytic cells.[5,6] Adiponectin may improve metabolic disorders, including those associated with SLE, due to these anti-inflammatory properties. Higher levels of circulating adiponectin in SLE patients correlate positively with inflammatory markers,[7] and SLE patients are reported to have higher serum adiponectin than healthy controls, while SLE patients with renal dysfunction are reported to exhibit higher serum levels than SLE patients without renal dysfunction.[8]

Several studies reports elevated values of leptin and adiponectin in SLE patients.[4,8,] however there was no clear explanation about the exact cause of such increased values. Additionally, the results were varied among patients according to demographic data, BMI or dietary components, disease markers and disease activity.[6] In light of these strong associations with SLE, this study examined if serum levels of adiponectin and leptin in Egyptian SLE patients are associated with disease activity and clinical manifestations.

Patients and methods

This case control study included 70 SLE patients who were diagnosed according to the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for SLE,[9] either hospitalized and/or in outpatient care at the Rheumatology and Rehabilitation Department of Beni-Suef University Hospital from June 2020 till April 2022. In addition, 50 healthy individuals matched for age and sex were included as controls.

Exclusion criteria

Patients with younger than 18 years old, pregnancy, malignancies, metabolic disorders, and patients undergoing hemodialysis or with a history of kidney transplantation were also excluded

The study was approved by the ethics committee of the Faculty of Medicine, Beni-Suef University (FMBSUREC/01092020/Mousa), and according to the ethical guidelines of the Declaration of Helsinki. Informed written consent was obtained from all participants after the study objectives were explained. Confidentiality of patient data was guaranteed.

Full medical histories were compiled for all patients. All study subjects received thorough clinical examinations and results of laboratory test were all data collected from the medical record. Body mass index (BMI) was measured as weight in kg divided by height in m^2.[10]

Routine laboratory measures included erythrocyte sedimentation rate (ESR), complete blood count, serum antinuclear antibody (ANA) and anti-double stranded DNA (anti-dsDNA) concentrations, and serum complement (C3 and C4) levels. Serum markers of liver function (alanine transaminase and aspartate transaminase concentrations in U/L, and serum albumin concentration [in g/dL]), serum markers of kidney function (serum creatinine and blood urea [in mg/dL]), and serum lipid profiles (total cholesterol, total triglycerides [TG], high-density lipoproteins, and low-density lipoproteins, all in mg/dL) were also measured. Complete urine analysis was performed for proteinuria (g per 24 h), RBCs, WBCs, and casts. Finally, renal biopsies were performed to confirm the presence of LN.

Clinical disease activity was assessed using the SLE disease activity index (SLEDAI), which grades manifestations based on presence or absence within 10 days of evaluation.[11] Disease severity was assessed using the

Systemic Lupus International Collaborative clinics/America Collage of Rheumatology (SLICC/ACR) damage index, a measurement of cumulative end organ damage described as non-reversible change, not related to active inflammation, occurring since the onset of lupus, and ascertained by clinical assessment.[12] Serum adiponectin and leptin concentrations were measured using the ELISA technique, in a typical capture assay "sandwich," according to the manufacturer's instructions (catalog numbers CAN-APN-5000 and CAN-L.4260; Diagnostics Biochem Canada Inc).

Statistical analysis

All statistical analyses were conducted using SPSS (version 20). Normally distributed continuous variables according to the X test are expressed as mean ± standard deviation, non-normally distributed variables as median with range, and dichotomous variables as frequency and percentage. Two independent group means were compared by the Mann–Whitney U-test, more than two independent group means by the Kruskal–Wallis test, and frequencies by chi-square test. Associations were evaluated by Pearson's or Spearman's correlation analysis as indicated. Receiver operating characteristic (ROC) analysis was used to examine the sensitivity, specificity, positive predictive value, and negative predictive value with which serum leptin and adiponectin distinguish patients from health controls. A $p \leq 0.05$ was considered statistically significant for all tests.

Results

The SLE patient group consisted of four males (5.7%) and 66 females (94.3%) ranging in age from 18 to 47 years (28.3 ± 9 years). Median disease duration was 3 years (range, 1–20 years) and mean BMI was 24.3 kg/m^2. *The demographic and anthropometric data* are summarized in Supplementary Table 1**.** The most frequent clinical manifestations were malar rash (97.1%), photosensitivity (97.1%), oral ulcers (68.6%), LN (61.4%), arthritis (47.1%), and serosistis (45.57%). Of the 43 LN cases confirmed by renal biopsy, 39.5% were class II, 20.9% had class doses, 90% were taking hydroxychloroquine, 31.4% cyclophosphamide, 65.7% azathioprine, and 2.8% mycophenolate mofetil. The SLEDAI ranged from 2 to 30 and was above the accepted SLICC cut-off in 15.7% of cases. Clinical and laboratory data of patients are summarized in Supplementary Table 2.

Median serum leptin was significantly higher in SLE patients than healthy control subjects (21.1 vs 3.9 ng/mL, $p < 0.001$). Similarly, median serum adiponectin was significantly higher in patients than controls (18.1 vs 4.8 ng/mL, $p < 0.001$) (Table 1). Moreover, both serum leptin and adiponectin levels were positively correlated with SLEDAI score in SLE patients ($p = 0.048$ and $p = 0.042$, respectively) (Figure 1). Higher serum leptin and adiponectin concentrations were also significantly associated with LN ($p = 0.048$ and $p = 0.046$). While there were no other significant associations with clinical manifestations (Table 2), serum leptin was also positively correlated with BMI, ESR, TG, uric acid, and CRP in SLE cases (Table 3).

ROC curves revealed that both serum leptin and adiponectin concentrations distinguished patients from controls with high accuracy (AUC = 0.972 and 0.833, respectively). At a cut-off value of 9.9 ng/mL, leptin distinguished patients from controls with 90% sensitivity, 92% specificity, 94% PPV, 86.8% NPV, and 90.8% accuracy, while an adiponectin cut-off value of 9.4 ng/mL distinguished patients from controls with 80% sensitivity, 82% specificity, 86.2% PPV, 74.5% NPV, and 80.8% accuracy (Figure 2).

Univariable linear regression analysis identified old age, gender, disease duration, and serum C3, C4, anti-ds DNA, leptin, and adiponectin levels as significantly associated with SLEDAI score, while multivariable analysis identified lower C4, higher serum leptin, and higher serum adiponectin as significant independent predictors of higher SLEDAI score (greater disease activity) (Table 4).

Discussion

Numerous cytokines, including interleukin (IL)-2, IL-4, IL-6, interferon gamma, and tumor necrosis factor (TNF)-alpha, and adipokines such as leptin, adiponectin, resistin, and visfatin are elevated in SLE.[13] Historically, adipose tissue has been considered largely inert physiologically and pathologically but is now known to participate in immunity and inflammation through section of adipokines, cytokines, and chemokines that act both locally and systemically.[11] For instance, adipocyte-derived immunomodulators (adipokines) have been implicated in the regulation of insulin sensitivity, appetite, and satiety, in bone metabolism and reproductive function, and in atherosclerosis as well as immunity and inflammation.[14]

Table 1. Comparison of serum leptin and adiponectin levels between with systemic lupus erythematosus (SLE) and control subjects.

	Control		SLE		
	n = 50		*n* = 70		
	Median	Range	Median	Range	*p*
Leptin	3.9	1.1–12.5	21.1	4.2–129.1	**<0.001**
Adiponectin	4.8	1.3–13.7	18.1	3.1–90.4	**<0.001**

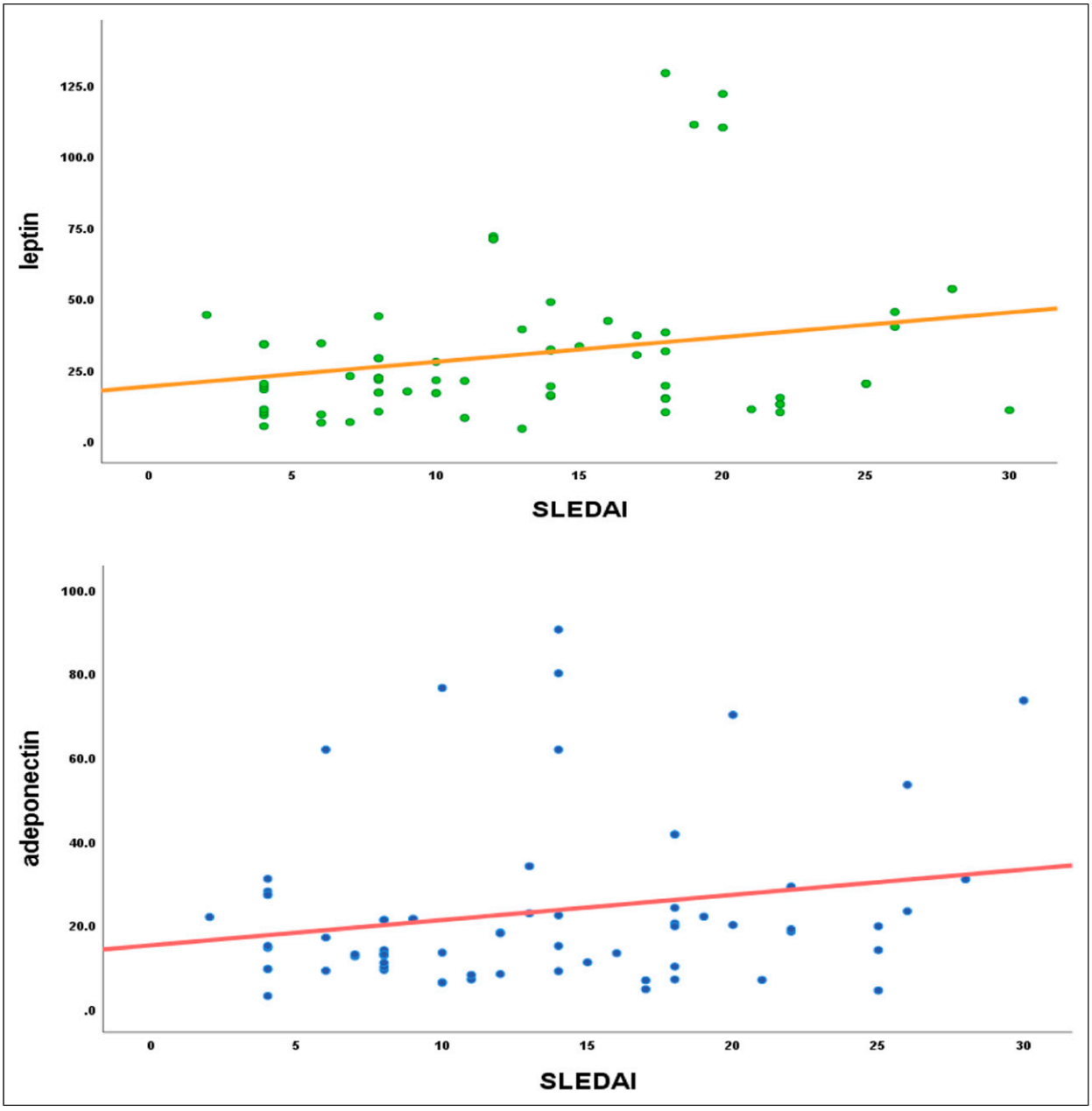

Figure 1. Correlations of serum leptin and adiponectin with systemic lupus erythematosus (SLE) severity (as measured by SLE disease activity index score).

Leptin is a pro-inflammatory adipokine that contributes to the inflammation associated with rheumatological diseases such as SLE[15] by increasing autoantibody production and inhibiting immune regulation pathways by promoting the proliferation and activation of T lymphocytes and induces production of Th1 cytokines. Further, leptin has also been implicated in metabolic syndrome and accelerated atherosclerosis among SLE patients by increasing the inflammatory biomarkers of atherosclerosis such as piHDL, Lp(a), and OxPL/apoB100.[15] Conversely, adiponectin has been shown to regulate glucose levels, lipid metabolism, and insulin sensitivity through anti-inflammatory, anti-fibrotic, and antioxidant effects.[16] In this work, we show that both serum leptin and adiponectin are elevated in SLE patients and independently associated with several clinical manifestations and markers of disease activity.

In accord with these findings, several recent studies have found significantly greater serum leptin concentrations in SLE patients compared to matched healthy controls in diverse populations from the Middle East and South

Table 2. Associations of serum leptin and adiponectin with clinical manifestations of SLE.

		Median adiponectin concentration (ng/mL)	*p*	Median leptin concentration (ng/mL)	*p*
Malar rash	**Absent**	7.55	0.229	14.5	0.521
	Present	18.3		21.25	
Discoid rash	**Absent**	18.1	0.641	20.5	0.685
	Present	17.4		25.65	
Photosensitivity	**Absent**	18.05	0.692	23.15	0.683
	Present	18.1		21.1	
Oral ulcers	**Absent**	21.2	0.840	25.2	0.350
	Present	17.5		20	
Arthritis	**Absent**	18	0.119	21	0.803
	Present	18.2		21.3	
Hematologic	**Absent**	18.3	0.215	20.6	0.556
	Present	13.2		24.35	
Serositis	**Absent**	18.7	0.212	19.65	0.118
	Present	14.3		22.4	
Alopecia	**Absent**	18	0.481	22.1	0.389
	Present	18.4		15.1	
Fever	**Absent**	17	0.143	21.2	0.450
	Present	23.3		10.7	
Neurologic	**Absent**	18.1	0.120	21.25	0.401
	Present	42.05		20	
Vasculitis	**Absent**	18.2	0.415	21.2	0.363
	Present	9.3		10.2	
Nephritis	**Absent**	13	**0.046**	19.1	**0.048**
	Present	21.2		29	

Table 3. Correlations of serum leptin and adiponectin with clinical parameters of SLE.

	Leptin		Adiponectin	
	Rs	*P*	Rs	P
Age	0.155	0.283	−0.147	0.225
BMI	0.304	**0.010**	−0.119	0.325
Duration	0.126	0.298	−0.097	0.425
TLC	0.204	0.091	0.061	0.616
HG	0.110	0.367	0.080	0.509
PLT	0.020	0.870	0.217	0.071
ESR	0.368	**0.002**	0.053	0.665
ALT	0.106	0.382	−0.164	0.127
TG	0.041	0.736	−0.189	0.118
Cholesterol	0.296	**0.013**	0.083	0.498
LDL	0.233	0.052	0.093	0.445
HDL	−0.174	0.149	0.155	0.199
C3	0.131	0.280	−0.196	0.105
C4	−0.001	0.994	−0.002	0.985
UA	0.358	**0.002**	0.041	0.735
Cr	0.014	0.910	0.085	0.486
UREA	0.076	0.529	−0.009	0.941
CRP	0.351	**0.003**	0.116	0.340
24 h proteinuria	0.089	0.537	0.043	0.765
Prednisolone dose	−0.034	0.783	0.169	0.161
Hydroxychloroquine dose	0.022	0.855	−0.093	0.443

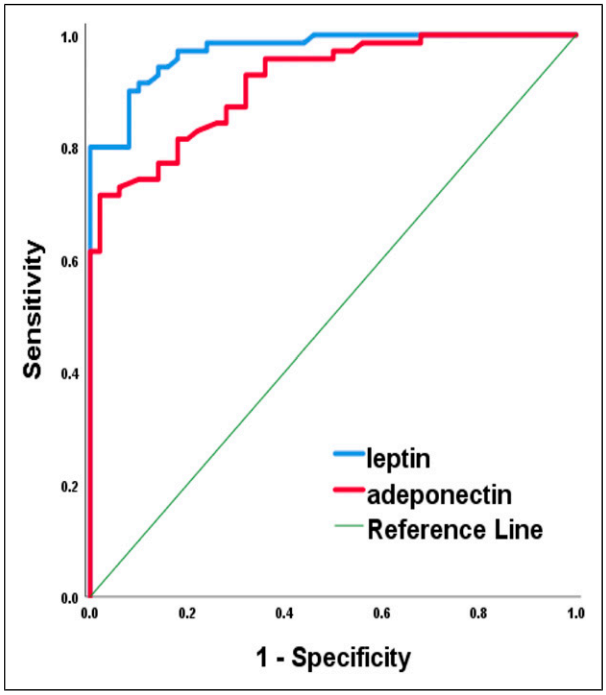

Figure 2. Receiver operating characteristic curve of serum leptin and adiponectin for discrimination of SLE from healthy controls.

Table 4. Regression analysis for prediction of activity of SLE cases (higher SLE disease activity index score).

	Univariable		Multivariable	
	B	*P*	*B*	*P*
Age	0.150	0.124	-	-
Gender	4.091	0.280		-
Disease duration	0.430	0.158	-	-
C3	−0.98	**<0.001**	−0.019	0.482
C4	−0.563	**<0.001**	−0.479	**<0.001**
Anti-ds DNA	6.809	**<0.001**	1.868	0.235
Leptin	0.085	**0.042**	0.058	**0.025**
Adiponectin	0.064	**0.048**	0.063	**0.045**

America.[13,17,18] Further, a meta-analysis of 18 studies comprising 1333 patients and 1048 controls found leptin elevation among SLE patients irrespective of ethnicity.[17] However, an earlier study from Poland found no such difference.[18] Also, Reagan et al. found numerically higher serum leptin levels in an SLE group that did not reach statistical significance.[6] Sample size, patient demographics, clinical heterogeneity, and therapeutic effects may account for these differences. However, we also found that serum leptin was significantly and positively correlated with disease activity as measured by the SLEDAI, providing support for a direct contribution to pathogenesis. Similarly, both Wang and colleagues and Vadacca and colleagues reported positive correlations between serum leptin and SLEDAI score.[19,20] However, Afifi and colleagues found no such correlation, again possibly due to heterogeneity within and among clinical populations as SLE symptoms are inherently variable and study inclusion criteria and treatment profiles (e.g., steroid doses) have varied across studies. Thus, additional studies of sufficient scale for careful subgroup analyses are needed to confirm our findings.

The current study also found that serum leptin level was significantly associated with LN, in accord with previous studies by Mohammed et al.,[21] Kim et al.,[22] and Barbosa et al.[17] In fact, Barbosa et al. found that renal involvement was the only clinical manifestation associated with increased leptin levels.[23] In contrast, Diaz-Rizo et al. found no difference in serum leptin levels between LN and non-LN patient groups.[24] In the present study, serum leptin was positively correlated with both markers of metabolic disease (BMI, ESR, total cholesterol, and uric acid) and inflammation (CRP) in SLE, as leptin is able to promote CRP production from hepatocytes and endothelial cells in vitro, and clinical studies showed a direct association between CRP and leptin plasma levels in healthy volunteers and people with obesity and type 2 diabetes mellitus.[20] Also, serum leptin level was positively correlated with metabolic syndrome. People with metabolic syndrome were mostly female and had higher BMI, serum BUN, and serum CRP levels than those without metabolic syndrome.[20]

Similarly, Mohammeda et al. and Chung et al. found significant correlations with BMI and total cholesterol among SLE patients.[21,25] On the contrary, Wislowska and colleagues found no correlation between serum leptin and total cholesterol.[18] Again, these discrepancies underscore the need for larger-scale studies permitting subgroup analyses to control for the effects of clinical heterogeneity.

We also found a significant difference in serum adiponectin between SLE patients and healthy controls, in agreement with an updated meta-analysis of 56 studies involving a total of 4460 patients with SLE,[26] a study by Ali et al. in 2020 of 36 SLE patients and 36 healthy controls,[8] and a 2017 meta-analysis.[27] Alternatively, an earlier study by Vadacca and colleagues found no such difference.[28] Adiponectin is thought to act primarily as an anti-inflammatory signaling factor in inflammatory diseases, including SLE.[27] Reynolds et al. speculated that increased adiponectin concentration in SLE patients could represent a compensatory response against inflammation. However, other studies have suggested a role in activation of nuclear factor κB, a major stress-induced transcription factor.[29]

Adiponectin possesses several beneficial activities, including anti-inflammatory, vascular protective, and anti-diabetic effects, although these properties may be a compensatory mechanism under chronic inflammation.[26] We also found that like serum leptin, serum adiponectin was positively correlated with SLEDAI. Similarly, Diaz-Rizo and colleagues observed a positive correlation between adiponectin and SLEDAI score,[24] but Ali et al. found no statistical correlation.[8] Higher serum adiponectin was significantly associated with LN and was an independent risk factor for LN, which may be explained by positive correlation between plasma adiponectin levels and proteinuria[30] and the renoprotective role of adiponectin by enhancing the AMPK/PPARα pathway suggesting a protective and compensatory role for adiponectin in mitigating further renal injury.[31]

In agreement, Diaz-Rizo et al. observed that higher serum adiponectin was associated with LN in SLE patients.[24] These findings are also consistent with Rovin and colleagues, who reported high plasma adiponectin in SLE with renal flare than SLE without renal flare.[32] Also, Loghman and colleagues observed higher urinary adiponectin in SLE patients with renal involvement and that urinary SLE is a useful biomarker to discriminate impaired from normal renal function in SLE patients.[33] Hutcheson et al. also observed increased serum adiponectin and leptin in SLE patients with LN compared to healthy controls,[34] supporting a sensitive adipokine-mediated interrelation

between adipose tissue, metabolic disorders, and autoimmune disorders.[21]

Finally, ROC analysis revealed that both leptin and adiponectin levels can accurately distinguish patients from controls. Similarly, Ali and coworkers and Rezaieyazdi and coworkers found that serum adiponectin accurately predicted SLE activity with renal involvement.[8,35]

Limitation

The main limitation of this study was we did not conduct any power analysis to calculate the sample size selected for this study.

Conclusion

Serum leptin and adiponectin levels are significantly elevated in SLE patients compared to healthy controls, associated with LN, and positively correlated with disease severity as measured by the SLEDAI, suggesting direct involvement in disease pathology and utility as disease biomarkers. Understanding the functions of leptin and adiponectin in SLE-associated inflammation may lead to the development of new therapeutic strategies targeting.

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Authors' contributions

All authors contributed to the design and interpretation of the data; SK, ME and EA follow up patients, EM and MK performed analysis, SK wrote the paper, ME, EA and MK revised it. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

Ethical approval for this study was obtained from the ethics committee of the Faculty of Medicine, Beni-Suef University (FMBSUREC/01092020/Mousa), and according to the ethical guidelines of the Declaration of Helsinki. Informed written consent was obtained from all participants after the study objectives were explained. Confidentiality of patient data was guaranteed.

Availability of data and materials

All data and materials are available and can be submitted when needed

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Supplemental material

Supplemental material for this article is available online.

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