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Elevated Serum Levels of CTRP-6 and Asprosin in Systemic Lupus Erythematosus: Association with Oxidative Stress Markers and Clinical Manifestations

Ali Hussein Hadi Nassar Al-Tamimi[1,2], Nadia Heydari[1,2], Saeed Mohammadi[3], Nafiseh Abdolahi[4], Seyyed Mehdi Jafari[1,2*]

[1]Metabolic Disorders Research Center, Biomedical Research Institute, Golestan University of Medical Sciences, Gorgan, Iran; [2]Department of Biochemistry and Biophysics, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran; [3]Immunology Laboratory, Natural and Medical Sciences Research Center, University of Nizwa, Nizwa, Oman; [4]Golestan Rheumatology Research Center, Golestan University of Medical Science, Gorgan, Iran

ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease that affects multiple organ systems. The resulting inflammation disrupts adipocyte metabolism, thereby altering the levels of adipokines.

Objective: To assess e serum levels of Asprosin and CTRP-6 as novel adipokines in SLE patients compared to controls, and their association with lipid profiles, oxidative stress markers, and clinical parameters.

Methods: This case-control study involved 41 SLE patients and 41 healthy controls. Serum CTRP-6 and Asprosin levels were measured using ELISA, while total antioxidant capacity (TAC) and malondialdehyde levels were measured using a colorimetric assay.

Results: The mean serum CTRP-6 level was significantly higher in individuals with SLE (1.08±0.32) compared to healthy subjects (0.82±0.21; $p<0.001$). Similarly, the serum level of Asprosin was elevated in patients with SLE (11.91±3.09) compared to the control group (10.28±2.09; $p<0.001$). In contrast, the TAC level was lower in subjects with SLE than in healthy controls (0.18±0.23, 0.19±0.51 respectively; $p<0.001$). Additionally, the serum level of Asprosin was significantly reduced in SLE patients with nephritis (10.17±3.55) compared to those without nephritis (12.4±2.75; $p=0.005$).

Conclusion: Elevated levels of Asprosin and CTRP-6 suggest a potential role for these adipokines in SLE pathogenesis. Moreover, the presence of nephritis in SLE patients was associated with reduced plasma levels of Asprosin.

Keywords: CTRP-6, Asprosin, Systemic Lupus Erythematosus

*Corresponding author:
Seyyed Mehdi Jafari,
Department of Biochemistry and Biophysics, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran
Email: s.meh.jafari@goums.ac.ir

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by inflammation and abnormal immune cell function, both of which are closely associated with metabolic dysregulation and alterations in adipokines levels (1-4).

C1q/tumor necrosis factor-related protein 6 (CTRP-6) and Asprosin, are recently identifiedadipokines (5, 6). CTRP-6 plays a crucial role in the pathogenesis of metabolic disorders, particularly those linked to chronic inflammation (7-9). It has been shown to directly affect adipocyte function by promoting the release of pro-inflammatory cytokines, such as TNF-α and IL-6, thereby contributing to the amplification of systemic inflammation (10).

Asprosin is associated with metabolic processes and inflammation (11-13). Its inflammatory effects are mediated, at least in part, through the activation of cytokines such as TNF-α and IL-6 (11).

Given the roles of CTRP-6 and Asprosin in regulating inflammation and metabolism, and considering that inflammation and metabolic disorders contribute to SLE pathogenesis, we investigated serum levels of CTRP-6 and Asprosin and their correlation with metabolic factors in SLE patients. Understanding the involvement of these adipokines may offer novel insights into the complex immunopathogenesis of SLE.

MATERIAL AND METHODS

A total of 41 patients diagnosed with SLE (37 women and 4 men) and 41 age- and sex-matched healthy controls (37 women and 4 men) were enrolled in this case-control study. The sample size was estimated based on a pilot study of 10 participants, with a mean±SD of 13.45±1.58 for Asprosin in SLE patients and 11.98±1.24 for control group. Using G Power 3.1 software (Edgar Erdfelder, Franz Faul, Albert-Georg Lang, and Axel Buchner; Germany), with a statistical power of 0.95 and an alpha error probability of 0.05, the minimum required sample size was calculated to be 26. SLE diagnosis was based on the American College of Rheumatology's updated criteria, requiring the presence of at least four of eleven clinical and laboratory manifestations (14). Written and oral informed consent was obtained from all participants. Exclusion criteria included renal failure, type 2 diabetes, arteriosclerosis, polycystic ovary syndrome, metabolic syndrome, heart disease, cancer, and recent pregnancy. The study was approved by the Ethics Committee of the Golestan University Faculty of Medicine (Ethical Code: IR.GOUMS.REC.1401.186).

Biochemical Analysis

CTRP-6 levels were determined using a ZellBio GmbH ELISA kit (Germany). The assay employs pre-coated plates with a capture antibody to detect biotin-conjugated antibodies. Following the addition of samples, standards, and biotin-conjugated detection antibodies, wells were washed to remove unbound conjugates before HRP-Streptavidin was added. After a subsequent wash, TMB substrate was used to visualize the HRP enzymatic reaction; the resulting yellow color intensity was inversely proportional to the CTRP-6 concentration, according to the manufacturer's instructions. Similarly, Asprosin levels were measured using a ZellBio GmbH ELISA kit (Germany). Serum was added to wells pre-coated with a monoclonal anti-Asprosin antibody, followed by biotin-labeled anti-Asprosin antibodies, which bind to streptavidin-HRP, forming an immunological complex. Unbound enzyme was removed by washing after incubation. An acid-induced reaction converted the solution from blue to yellow. Malondialdehyde (MDA) and Total Antioxidant Capacity (TAC) were also evaluated using Zellbio GmbH kits (Germany) according to the manufacturer's instructions.

Statistical Analysis

The Shapiro-Wilk test was used to assess

the normality of CTRP-6, Asprosin, MDA, and TAC levels. The Mann-Whitney test was used to compare two groups. Spearman and Pearson correlation tests were used to assess relationships among CTRP-6, Asprosin, and oxidative stress indicators.

RESULTS

This study compared 41 SLE patients with 41 healthy controls. The average age was comparable in the SLE group (27.95±5.90 years) and the control group (29.07±6.25 years) (p=0.406). Table 1 presents the laboratory findings and clinical characteristics of the SLE patients. Serum levels of both CTRP-6 (1.08±0.32 vs. 0.82±0.21) and Asprosin (11.91±3.09 vs. 10.28±2.09) were significantly elevated in SLE patients compared to controls (p<0.001, Fig. 1 and Fig. 2, respectively).

In SLE patients, adipokine overproduction is strongly correlated with oxidative stress (15). To assess oxidative stress, the levels of MDA and TAC were evaluated. Subsequently, we examined the correlation of oxidative stress markers with CTRP-6 and Asprosin. No significant difference in MDA levels was found betweenSLE patients and controls. Serum TAC levels were lower in SLE patients (0.18±0.23) than healthy controls (0.19±0.51, p<0.001). However, no significant correlation was observed between CTRP-6 and Asprosin and MDA or TAC (data not shown). Additionally, CTRP-6 and Asprosin showed no significant correlation with lipid profile (data not shown).

Table 1. Laboratory findings and clinical characteristics of SLE patients

Manifestation	SLE patients
Nephritis	24.3%
Malar rash	46.3 %
Hair loss	36.5%
Anti-dsDNA titre	105.02±63.23
WBC count (cells/µL)	5312.20±1128.538
ESR (mm/hr)	48.6098±16.77
RF-IgG (IU/mL)	49.39±28.81
SLEDAI score	14.43±14.087

Anti-dsDNA, anti-doublestranded DNA; WBC count, White Blood Count; ESR, Erythrocyte Sedimentation Rate; RF-IgG, Rheumatoid Factor IgG; SLEDAI, systemic lupus erythematosus disease activity index

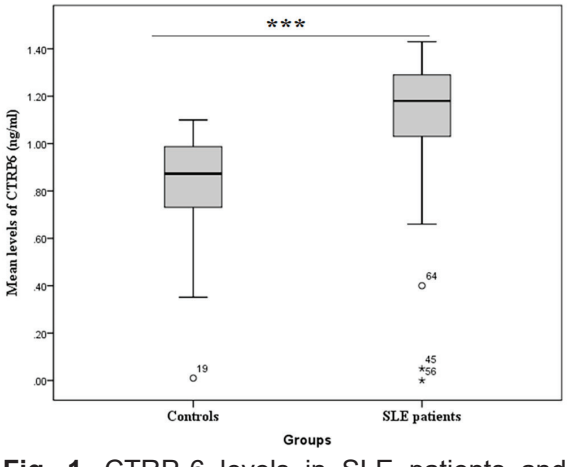

Fig. 1. CTRP-6 levels in SLE patients and the control group. Serum CTRP-6 levels were measured using ELISA. CTRP-6 levels were significantly higher in the SLE group compared to the control group. Error bar indicate standard deviation (***p<0.001).

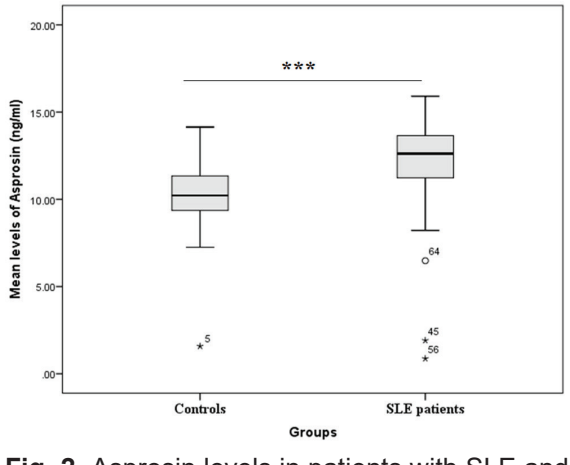

Fig. 2. Asprosin levels in patients with SLE and healthy controls. Serum Asprosin levels were measured using ELISA. The asprosin levels were significantly higher in the SLE group compared to the control group. Error bar indicated Standard deviation. (***p<0.001).

Table 2. CTRP6 levels in relation to clinical characteristics of patients

Variable	Number	CTRP6 (mean±SD)	*p value*
Nephrite (Positive)	10	0.96±0.38	0.095
(Negative)	31	1.12±0.30	
Malar rash (Positive)	19	1.03±0.39	0.456
(Negative)	22	1.13±0.26	
Hair loss (Positive)	15	1.05±0.39	0.807
(Negative)	26	1.10±0.29	

Table 3. Asprosin levels in relation to clinical characteristics of patients

Variable	Number	Asprosin (mean±SD)	*p value*
Nephrite (Positive)	10	10.17±3.55	0.005**
(Negative)	31	12.48±2.75	
Malar rash (Positive)	19	11.57±3.92	0.734
(Negative)	22	12.21±2.19	
Hair loss (Positive)	15	12.04±3.54	0.424
(Negative)	26	11.84±2.86	

Patients were divided into groups based on hair loss, malar rash, and nephritis (Tables 2 and 3). CTRP-6 and Asprosin levels did not significantly differ between groups based on hair loss or malar rash. Similarly, CTRP-6, MDA, and TAC levels also showed no significant difference between nephritis groups, Asprosin levels were decreased in patients with SLE nephritis (p=0.005). Furthermore, CTRP-6 and Asprosin levels showed no difference in SLE patients based on SLEDAI scores (above or below 10) and did not correlate with other laboratory findings (data not shown).

DISCUSSION

The current study's findings showed that Asprosin level is higher in SLE patients compared to control. The present study also showed that the CTRP6 level in patients with SLE is higher than in the control group. This data is supported by previous studies. According to research by Groener et al., patients with type 1 diabetes (an autoimmune disease) had higher Asprosin compared to the control group (16). Murayama et al. found that CTRP6 is elevated in the serum of patients with rheumatoid arthritis (14). Sanctis et al. found that adiponectin, ghrelin and visfatin levels were increased in SLE patients (17). Chouglue et al. reported that progranulin, resistin and adipsin levels were higher in SLE patients (18). Some research contradicts our study. Sanctis et al. found that leptin levels were decreased in SLE patients (17). Chouglue et al. reported that omentin levels were lower in SLE patients in comparison with controls (18). Overall, the findings of current research suggest that evaluating Asprosin and CTRP6 may open new windows for diagnosing and managing SLE.

Serum MDA levels were elevated in SLE patients compared to controls, although the difference was not statistically significant. Conversely, serum TAC levels were lower in the SLE group compared to the control group, consistent with previous findings by Yilmaz et al. (19) and Hassan et al. (20). These results, in conjunction with others (21), indicate an imbalance in the oxidant/antioxidant equilibrium in SLE patients, characterized by a decrease in total antioxidant capacity and an increase in MDA levels.

While previous studies have suggested

that CTRP-6 and asprosin are linked to oxidative stress and lipid profiles (22-24), no significant relationship was observed in the study participants. Differences between SLE and metabolic disorders, such as lipid status, warrant consideration.

In patients with systemic lupus erythematosus (SLE), serum Asprosin levels were significantly higher in those without nephritis compared to those with nephritis, suggesting a potential role for Asprosin in lupus-related kidney dysfunction. One study reported decreased omentin levels in SLE patients with renal manifestations (25), while others found elevated levels of adiponectin, resistin, and leptin in lupus nephritis (26). However, some studies showed no statistical difference in leptin levels between SLE patients with and without nephritis (27). These conflicting findings regarding adipokines in lupus patients with and without nephritis emphasizes the need for further mechanistic research to investigate their role and association with nephritis in lupus.

CONCLUSION

SLE patients showed elevated serum levels of Asprosin and CTRP-6. The results of this study suggest that Asprosin and CTRP-6 plays a significant role in the pathophysiology of SLE. Serum Asprosin levels were found to be decreased in SLE patients without nephritis, indicating its potential as a useful biomarker for predicting renal involvement. However, this study is limited by its small sample size and the inclusion of patients with various types of renal involvement. Further research with a larger patient sample is necessary to clarify the roles of CTRP-6 and Asprosine in lupus development, as well as their potential as diagnostic and therapeutic targets. Future studies investigating CTRP-6 and Asprosin levels in SLE patients should take into account inflammatory factors. Longitudinal measurement of Asprosin and CTRP-6 levels during treatment and follow-up is also recommended. Additionally, exploring the signalling pathways modulated by Asprosin and CTRP-6 in immune cells could provide insights into the mechanisms underlying their involvement in SLE.

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AUTHORS' CONTRIBUTION

Ali Hussein Hadi Nassar Al-Tamimi conducted the experiment and drafted the manuscript. Nadia Heydari organized the methodology and performed the data analysis. Saeed Mohammadi and Nafiseh Abdolahi contributed to sample collection. Moreover, Seyyed Mehdi Jafari was responsible for the study design.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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