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Assessment of Serum Leptin in Patients with Chronic Spontaneous Urticaria

Mohamed Nazmy Farres, Mayada Moneer Mahmoud, Nouran Mohamed Eissa, Hossam Moustafa Elkady*
Department of Internal Medicine, Allergy and Clinical immunology,
Faculty of Medicine, Ain Shams University, Cairo, Egypt.
***Corresponding author:** Hossam Moustafa Elkady, **Phone:** (+2) 01090751701, **E-mail:** hossamelkady86@ymail.com

ABSTRACT
Background: Chronic spontaneous urticaria (CSU) is an inflammatory skin disease. The pathogenesis of CSU is still not completely understood in most cases. The association between CSU and obesity suggests a potential role for adipokines, mainly leptin, which have variable proinflammatory function.
Objective: To assess serum leptin levels in CSU patients and their relation to disease activity.
Patients and Methods: A case-control study, involving 60 patients with chronic spontaneous urticaria and 30 controls, was conducted at the Allergy Clinic of Ain Shams University hospital. CSU patients were graded as mild, moderate, and severe according to urticaria activity score 7(UAS7). The serum leptin levels were compared among different study groups. **Results:** Serum leptin levels were significantly higher among CSU patients than control group ($p<0.001$), with a positive correlation with urticaria activity (P value <0.001 and $r = 0.691$).
Conclusion: Serum leptin levels are increased in CSU, leptin could have an important role in the pathogenesis of CSU.
Keywords: Serum leptin level, Chronic spontaneous urticaria (CSU), Urticaria activity score (UAS).

INTRODUCTION

Chronic urticaria (CU) is a mast cell skin disease, presented by at least six weeks of continuous or recurrent urticaria. CU is classified into chronic inducible urticaria and chronic spontaneous urticaria (CSU). CSU occurs in the absence of any exogenous trigger [(1)].

The urticaria activity score 7 (UAS 7) depends on symptoms documented by the patients, such as the number of wheals and severity of itching, to evaluate the disease activity [(1)].

CSU may be associated with overweight and obesity. Increased body mass can cause urticaria symptoms to develop later onset [(2)]. Also CU patients may exhibit one or more unidentified elements of the metabolic syndrome [(3)]. Mast cells which are the key cells in pathogenesis of CU [(4)], are involved in the metabolic syndrome [(5, 6)]. In metabolic syndrome, a lot of pro-inflammatory adipokines are overproduced [(7)]. This raises the possibility of a connection between adipokines and the pathophysiology of CU.

Adipocytes produce numerous proinflammatory adipokines such as leptin. Leptin not only regulates fat metabolism and appetite but also has immunomodulatory function. A lot of immune cells react to leptin through leptin receptors, resulting in proinflammatory status. Leptin also promotes the T helper 1 phenotype in T lymphocytes [(8-11)].

AIMS OF THE STUDY

In this study, we aimed to evaluate leptin levels in patients with chronic spontaneous urticaria and to outline the relationship between serum leptin and urticaria severity.

PATIENT AND METHODS

A case-control study was conducted at the Allergy and Immunology Outpatient Clinic at Ain Shams University hospital on 60 patients diagnosed as having chronic spontaneous urticaria according to the EAACI/GA2LEN/EDF/WAO guideline [(1)] and 30 disease-free controls who were group-matched with patients for age and sex, with no co-morbidity or allergic diseases. The body mass index was within the normal range for all participants.

Inclusion criteria: Patients aged 18 to 60 years with chronic spontaneous urticaria with normal body mass index.

Exclusion criteria: Physical (inducible) urticaria, other possible causes of chronic urticaria, and acute urticaria, patients on medication for the previous three months prior to recruitment (other than antihistamines), or patients on steroids or immunosuppressive drugs, pregnant women or patients with amenorrhea, patients with co-morbidity such as endocrine disorders (thyroid disorders), chronic infection, diabetes mellitus, hypertension, ischemic heart disease, malignant tumors, hepatic and renal disease, and other inflammatory skin diseases and patients who are overweight or obese (body mass index $\geq$ 25 kg/m2) or have a history of eating disorders.

All patients with chronic spontaneous urticaria were subjected to the following:

Full history taking and clinical examination, laboratory tests to rule out any possible causes of CU: Thyroid function tests, antithyroid antibodies, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and antinuclear antibody (ANA).

Evaluation of urticaria activity score (UAS 7):

Disease activity was defined according to EAACI/GA2LEN/EDF/WAO guidelines [(1)] by urticaria

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activity score 7. The UAS-7 assesses the two main urticaria symptoms, itching and hives (wheal). The UAS7 values of the patients were assessed for the last 7 days, depending on their wheal numbers and the intensity of itching. Then, the scores of pruritis and wheal were added up for seven days (minimum 0–maximum 42). (UAS7 ≤ 6 is a controlled case, 7–15 is a mild case, 16–27 is a moderate case, and 28–42 is a severe or intense case) [(1)].

Measurement of Serum leptin:

After an overnight fast of at least 8 hours, venous blood samples of all participants were taken, serum leptin level was measured by using enzyme-linked immunosorbent assay (ELISA) kits (Catalogue no: 201-12-1560, Sunred Biological Technology Co., Ltd., Shanghai, China).

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data was collected, reviewed, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. Means, standard deviations, and ranges were used to present the quantitative data. Additionally, qualitative variables were presented as numbers and percentages. Using the Chi-square test, groups with qualitative data were compared. A One-Way ANOVA test was used to compare more than two groups, followed by post hoc analysis utilising the LSD (least significant difference) test. Two quantitative parameters in the same group were correlated using Spearman correlation coefficients. At a p-value of < 0.05, the result was considered significant.

RESULTS

The current study was conducted on 60 CSU patients and 30 healthy controls. Of the 60 CSU patients, 78.33% were females and 21.67 % were males. All CSU patients were within the age group of 21–58 years. Of the 30 healthy controls, 76.66% were females and 23.33% were males. All controls were within the age group of 19–60 years (table **1**).

As shown in table (1), cases and controls were comparable in sex and age.

Table (1): The gender and age distributions of all study groups.

		Control group	patients group	P-value	
		No. = 30	No. = 60		
Age	**Mean±SD**	38.15 ± 11.82	35.37 ± 11.69	0.292	t test
	Range	19 - 60	21 – 58		
Gender	**Males**	7 (23.33%)	13 (21.67%)	0.933	Chi square test
	Females	23 (76.66%)	47 (78.33%)		

SD: standard deviation

As shown in table (**2**), BMI (body mass index) values were in the normal range for all cases and control with no significant difference.

Table (2): Comparison of body mass index among cases and controls**.**

		Control group	Patients group	t test
		No. = 30	No. = 60	P-value
Height (m)	**Mean±SD**	1.65 ± 0.04	1.67 ± 0.05	0.124
	Range	1.61 – 1.79	1.56 – 1.78	
Weight (kg)	**Mean±SD**	64.83 ± 3.09	65.85 ± 3.83	0.213
	Range	61 – 71	58 – 72	
BMI (kg/m2)	**Mean±SD**	23.67 ± 0.49	23.59 ± 0.88	0.646
	Range	21.85 – 24.28	20.96 – 24.86	

Serum leptin levels were significantly higher among CSU patients than controls (p value<0.001) (Table **3** & Figure **1**).

Table (3): Comparison of leptin levels among cases and controls

	Control group	Patients group	t test
	Mean ± SD	Mean ± SD	p value
Leptin level (ng/ml)	6.67 ± 3.12	15.71 ± 9.64	<0.001

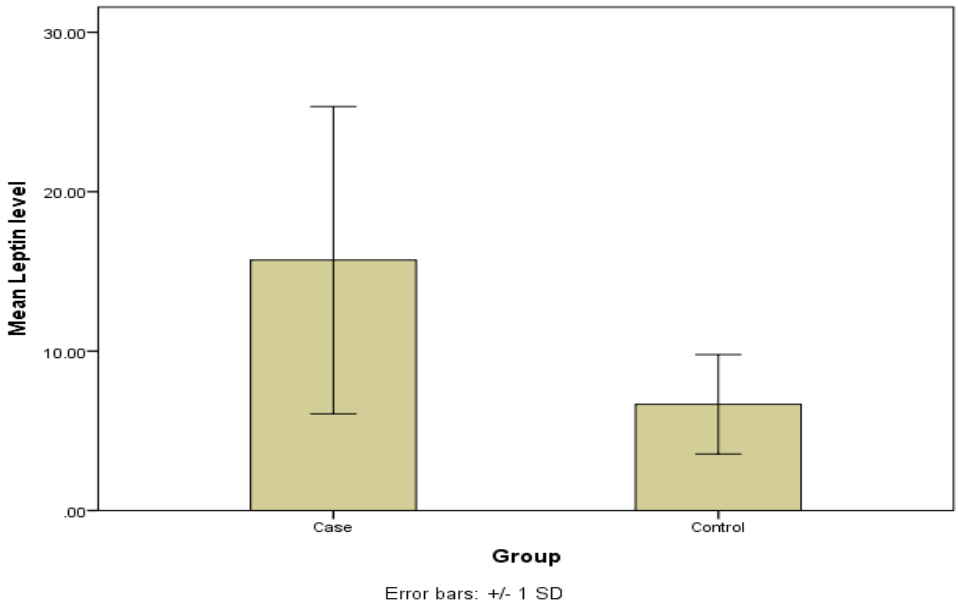

Figure (1): Leptin levels in cases compared to controls.

According to the UAS7 score, 13 CSU patients had mild disease, 24 had moderate disease, and 23 had severe disease. There is a significant relation between serum leptin levels and urticaria activity score. Serum leptin levels were highest among cases with severe urticaria and lowest among cases with mild urticaria (Table **4** & figure **2**).

Table (4): Relation between leptin level and UAS

	UAS						ANOVA
	Mild (13 cases)		Moderate (24 cases)		Severe (23 cases)		
	Mean	SD	Mean	SD	Mean	SD	p value
Leptin level (ng/mL)	7.36	5.46	14.43	6.59	22.07	9.99	<0.001*

*Post hoc test: all levels of severity are significantly different from each other

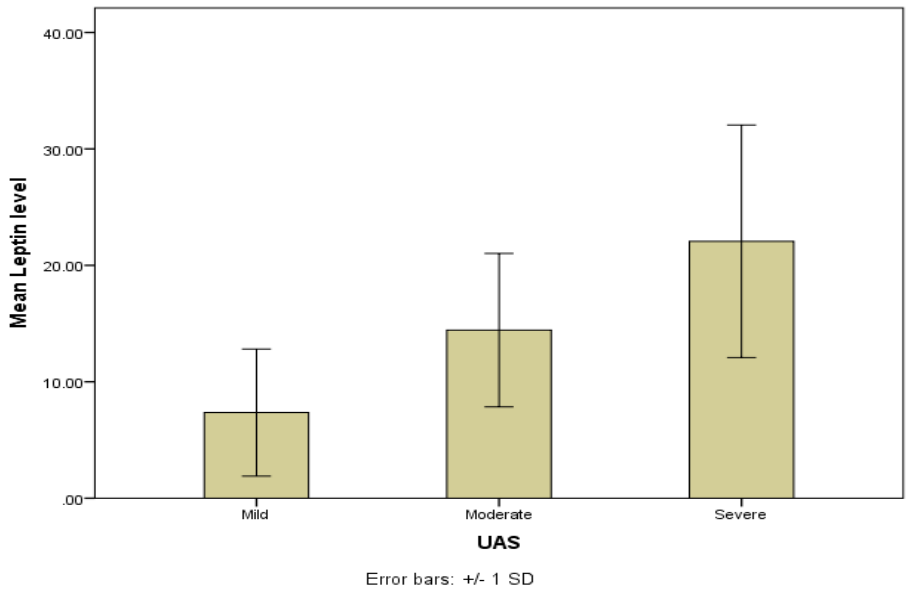

Figure (2): Leptin levels in relation to urticaria activity score

As shown in table (5), leptin levels showed a significant correlation with UAS among cases.

Table (5): Correlation between serum leptin and urticaria severity.

Among cases N=60		Leptin level
UAS	R	0.691
	p value	<0.001

This is a scatter plot chart showing that there is a positive correlation between urticaria activity score (UAS) and serum leptin with a P value <0.001 and r = 0.691(figure **3**).

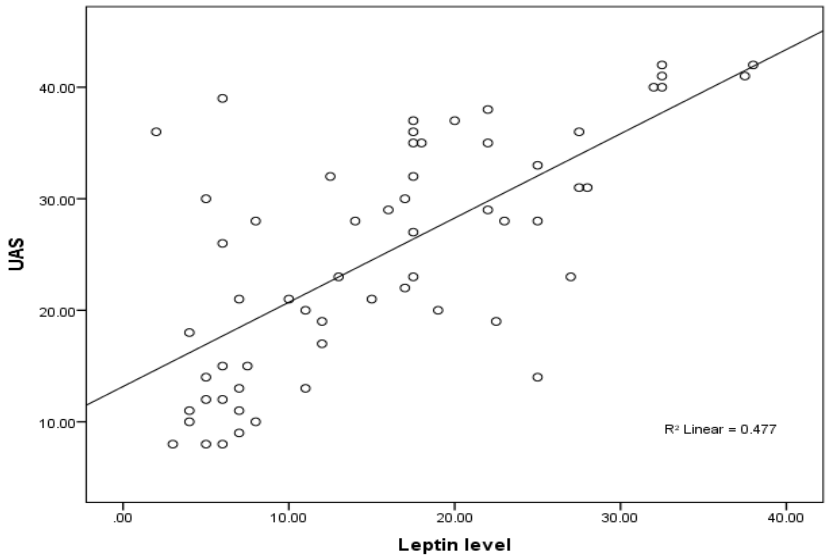

Figure (3): Correlation between urticaria activity score (UAS) and serum leptin.

DISCUSSION

There are two main subtypes of CU: chronic spontaneous urticaria and inducible urticaria. CU is described as a disease characterised by the development of recurring wheals and/or angioedema occurring for more than six weeks [(1)].

The main inflammatory cells in the pathophysiology of CSU are skin mast cells [(12)]. It is likely that mast cell activation in CSU is probably caused by inflammatory cascade activation and immune system dysfunction [(13)].

Since leptin had variable effects on immune system function, it was important to evaluate its role among CSU patients.

In the present study, the age of CSU patients was between 21–58 years; 78.33% were females and 21.67%were males. The reason for the female predominance in the present study is that women are more susceptible to chronic urticaria [(14)].

In the current study, we found that patients with CSU had a higher serum leptin level compared to control subjects. To our knowledge, there are very few previous studies that assessed serum leptin among CSU patients. In agreement with this result, **Garmendia *et al.*[(15)]** conducted a study on 32 CSU and 32 controls and demonstrated a higher level of serum leptin in CSU patients compared to controls. Also, **Fang *et al.*[(16)]** investigated serum leptin in 50 CU patients and 100 controls and found that 76% of the cases had high levels of serum leptin in comparison to controls. Regarding UAS7, we also found a significant positive correlation between leptin level and the severity of CSU.

In contrast, **Trinh *et al.*[(17)]** found no significant difference in the levels of serum leptin between CU and controls. Also, they found that serum leptin level did not correlate with urticaria activity. But the CSU patients were on treatment; some cases were on steroids or cyclosporin, which may affect the inflammatory pathway. Also, the body mass index had not been compared between cases and controls.

Limitation and strength of the study:

The limitations of this study included the relatively small sample size of the participants and the small number of cases in subgroups, so more studies on large numbers of patients are required.

The strength of the current study included that any known stimulus of chronic spontaneous urticaria was ruled out by history and adequate investigations for all patients. Furthermore, CSU patients and controls had normal BMI with no significant difference to rule out the effect of obesity on leptin levels.

CONCLUSION

In our study, we revealed that serum leptin levels are increased in chronic spontaneous urticaria with a positive correlation with urticaria severity. Therefore, leptin may have a role in the pathogenesis of CSU independent of obesity.

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