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Evaluation of Serum Leptin Level and Its Association with Disease Activity and Some Inflammatory Factors in Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND AND OBJECTIVE: Systemic lupus disorder is a heterogeneous autoimmune disease that can affect any organ of the body. Leptin affects the activation, differentiation and proliferation of immune cells. This study aimed to evaluate the serum level of leptin and its relationship with disease activity and some inflammatory factors in women with systemic lupus erythematosus (SLE).

METHODS: In this cross-sectional study, 40 women with SLE who were admitted to the rheumatology ward of Urmia Imam Khomeini Hospital during the second semester of 2017 and 40 healthy controls were enrolled. Serum leptin concentration was measured by sandwich ELISA method in two groups. In SLE patients the disease activity was calculated using Systematic lupus erythematous activity index (SLEDAI). Inflammatory factors including CRP (C-reactive protein) and ESR (Erythrocyte Sedimentation Rate) were extracted from the patient's records at the time of admission.

FINDINGS: Serum leptin level was significantly different in patients (44.51±25.6) and controls (22.37±12.58) ($p<0.001$). Also, Serum leptin level was significantly higher in the active phase than inactive phase of the disease (active phase: 67.13±24.88, inactive phase: 24.88±12.37) ($p<0.001$). There was a positive correlation among serum leptin and activity level ($r=0.7$, $p<0.001$), ESR ($r=0.53$, $p<0.001$) and CRP ($r=0.34$, $p=0.027$).

CONCLUSION: Leptin serum level is high in patients with systemic lupus erythematous and is positively associated with disease activity.

KEY WORDS: *Serum Leptin, Systemic Lupus Erythematosus, Active Phase, Inflammatory Factors.*

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Introduction

Systemic Lupus Erythematous (SLE) is a chronic autoimmune inflammatory disease that can affect many organs in the body. This disease is more common in women of childbearing age and genetic, immunological, hormonal and environmental factors are thought to be involved in its pathophysiology (1-4). The prevalence of SLE varies in different parts of the world and its prevalence is higher in Asian and African countries, so that it varies between 40 to 200 per 100,000 people (5). Its prevalence in the United States varies from 5.8 to 130 per 100,000 people, and in Japan it is 40.7 and in China between 31 and 70 per 100,000 people (6). Leptin is a 16 kDa hormone secreted by adipocyte cells and is part of the cyclic cytokines family such as interleukins 6, 11, and 12 (7, 8). This hormone causes a feeling of satiety in the body and controls body weight and is effective in glucose homeostasis by regulating the secretion of insulin and glucagon (9). In addition, this hormone is effective on the neuroendocrine system, bone formation, angiogenesis, and the inflammatory and immune response (10, 11).

Various physiological factors such as fasting, exercise and exposure to cold affect the serum level of leptin, each of which reduces the incidence of ob gene and thus reduces the level of circulating leptin. Serum leptin concentrations also change under conditions of large differences in energy intake, such as starvation or overeating. Serum leptin levels are also higher during the night (12).Plasma leptin levels are directly related to body mass index (BMI) (13). Recently, studies have shown that leptin plays a regulatory role in the central nervous system and is associated with pathological and physiological mechanisms of neurophysiological diseases, including neurological diseases and behavioral disorders (14, 15).

In obese individuals, plasma leptin levels are associated with inflammatory markers (reactive protein C, serum amyloid A and IL6) (16). Leptin is involved in the pathogenesis of autoimmune diseases (13). The relationship between serum leptin levels and SLE has been investigated in various studies (1, 17-19). One study showed that serum leptin levels were high in patients with systemic lupus erythematosus, which could be secondary to chronic inflammatory status or directly affect disease progression (18). However, some studies have concluded that there is no relationship between serum leptin levels and systemic lupus erythematosus (17, 19). Due to the contradictory results in previous studies, the aim of this study was to determine the serum leptin level in women with systemic lupus erythematosus and its relationship with disease activity and other inflammatory variables.

Methods

This cross-sectional study was approved by the Ethics Committee of Urmia University of Medical Sciences with the code IR.UMSU.REC.1390.78 and was performed on patients with systemic lupus who were admitted to the rheumatology department of Imam Khomeini Hospital in Urmia during the second semester of 2017 and according to the criteria ACR (American College of Rheumatology) (20) had definite lupus. Patients with diabetes mellitus and other endocrine diseases were excluded from the study. The control group was selected by convenience sampling method from healthy individuals with no history of inflammatory, endocrine or metabolic diseases who were referred to the hospital on an outpatient basis, and each patient in the patient group was matched with one person in the control group in terms of age, and finally 40 female patients with lupus and 40 individuals in the control group were included in the study. In all patients with lupus, scores related to disease activity were calculated using the SLEDAI (Systemic Lupus Erythematous Disease Activity Index) (21). After overnight fasting and obtaining written consent for both groups, blood samples were taken in the early morning hours and serum was kept at -20 ° C and serum leptin concentration were measured based on ELISA sandwich method using a factory-made kit ab179884 , Abcam Plc, Cambridge, UK .The tests were performed according to the manufacturer's instructions. According to the instructions, serum samples were diluted with normal saline at 1:40 and controls and samples were assayed twice. 50 µl of the whole sample or standard and 50 µl of antibody cocktail were added to the plates. The plates were incubated for 1 hour at room temperature in a plate shaker at 400 rpm. After that, each plate was washed with 350 × 3 µl. After the last wash, the plate was inverted and placed in front of clean paper towels to remove excess liquid. A curve was plotted for each standard concentration versus the target protein concentration. The minimum detectable dose was 4.65 pg / mL and the mean coefficient of variation between and within the experiments was 5.1 and 3.5%, respectively. The standard method for measuring ESR (Erythrocyte Sedimentation Rate) is the Western method, so using this method ESR was measured by an

analyzer (Sussex Ltd, Japan). CRP (C-reactive protein) was measured in patients using immunoassay by KA3640 Abnova, kit (Taiwan). Demographic information of all participants including age, duration of disease in patients and inflammatory factors including CRP, ESR and other laboratory values including (C3, C4 and Anti-ds DNA) were recorded at the beginning of hospitalization and in a checklist and analyzed. Analysis of variance (Anova) was used to compare the mean serum leptin level between patients (active and inactive disease) and the control group. Pearson correlation test was used to evaluate the relationship between serum leptin level with disease activity and inflammatory factors as well as other laboratory factors in patients and p <0.05 was considered significant.

Results

The results showed that there was no statistically significant difference between the mean age in patient group (29.68±7.86 years) and control group (28.78±5.86 years). Serum leptin level in patients (44.51±25.6) and control group (22.37±12.58) had a statistically significant difference (p<0.001) (Figure 1). Patients with lupus were divided into two groups (active and inactive) in terms of systemic lupus erythematosus disease activity. In the study of serum leptin in two groups of patients (active and inactive disease), the mean serum leptin in the group of patients with active disease (67.13±24.88) was significantly higher than patients with inactive disease (24.88±12.37) (p<0.001) (Table 1).

In the study of the correlation between serum leptin content with inflammatory factors and other laboratory variables in patients with SLE, the results showed that there was a significant positive correlation between serum leptin level and disease activity (r= 0.7 and p<0.001). ESR (r= 0.53 and p<0.001), CRP (r= 0.34 and p= 0.027) and serum amount of Anti-ds DNA (r = 0.33 and p = 0.03).While a significant negative correlation was obtained between the amount of serum leptin and the duration of the disease (r= -0.38 and p= 0.041) and the amount of serum C3 in patients (r= -0.32 and p= 0.043). Serum leptin levels in patients with serum C4 (r= 0.25 and p= 0.11) had no statistically significant correlation (Table 2).

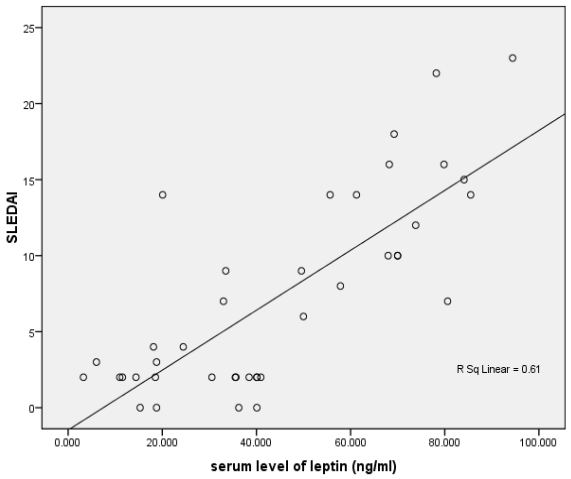

Figure1. Correlation between serum leptin and disease activity based on SLEDAI index in patients with SLE

Table 1. Comparison of mean age and serum leptin in SLE patients (active and inactive disease) and control group

Variables	Patient Group (Mean±SD)				P-value
	Active Disease	Inactive Disease	Total patients	Control Group	
Serum leptin level (ng/ml)	64.13±24.88	28.8±8.14	44.51±25.6	22.37±12.58	<0.001
Age (year)	30.55±7.68	28.8±8.14	29.68±7.86	28.78±5.86	0.56

Table 2. Correlation coefficient between serum leptin and measured variables in patients with SLE

Variables	Serum leptin levels	P-value
Duration of illness (months)	-0.38	0.014
Disease activity	0.7	<0.001
ESR	0.53	<0.001
CRP	0.34	0.027
C3 (mg/dl)	-0.32	0.043
C4 (mg/dl)	0.25	0.11
Anti-ds DNA	0.33	0.03

Discussion

The findings of the present study showed that serum leptin level in patients with lupus was significantly higher than the control group and among patients in the active phase was higher compared to patients in the inactive phase of the disease. Also, a positive correlation was found between serum leptin level and disease activity, inflammatory factors such as ESR and CRP and serum Anti-ds DNA level. In Reagan et al.'s study, it was shown that serum leptin level in SLE patients were higher than the control group, but this difference between the two groups was not significant and no significant relationship was observed between leptin level and disease activity (1).

The lack of association between leptin level and disease activity in the Reagan study may be due to a smaller sample size than in the present study. Serum leptin levels are also correlated with disease activity, while they are inversely correlated to regulatory T cell proliferation (CD4 cells) (19, 22, 23). Leptin increases T-cell proliferation and differentiation into helper 1 T cells, so that by administering glucocorticoids to patients with lupus, the number of helper 1 cells decreases and the number of helper 2 cells increases (24). In the study of Mohammed et al., serum leptin levels in SLE patients were significantly higher than the control group (25).

Serum leptin levels in patients with lupus with different genotypes in terms of leptin gene and its receptor are not significantly different (11). In another study, Li et al. found that serum leptin levels in patients with lupus were not significantly higher than in healthy individuals, but in a specific Asian population over 40 years of age with a body mass index of less than 25, significantly was higher (26). Leptin is involved in the regulation of body weight and energy balance, and in obese individuals, plasma leptin levels are associated with inflammatory markers (reactive protein C, serum amyloid A and IL6) (16).

Consistent with the results of the present study in a study conducted by Vadacca et al., it was shown that leptin levels in SLE patients were significantly higher than those in the control group. There was also a positive correlation between leptin levels and disease activity (27). In another study, Afroze et al. showed that serum leptin levels in SLE patients were significantly higher than the control group. In addition, it was shown that SLE patients had significantly higher BMI at high leptin quartiles (<32.5 ng / Ml) (28). The difference between the Afroze study and the present study is that in the present study, the body mass index of the study participants was not studied and the higher leptin level in patients may be due to their obesity compared to the control group, but due to the fact that Active and inactive diseases have also been compared, so this relationship is somewhat generalizable. Another meta-analysis study showed that leptin levels in SLE patients were higher than the control group (29).

In the present study, a positive correlation was observed between serum leptin levels and inflammatory factors (ESR and CRP). Consistent with the present study, Badawi et al. showed that there was a positive association between leptin and ESR in SLE patients (30). In general, leptin has inflammatory properties and activities like other acute phase reactants and regulates the secretion of several inflammatory cytokines, including TNF-α, IL-6, and IL-1 (31).

In summary, it seems that the serum leptin level in patients with systemic lupus erythematosus is significantly higher than healthy individuals and also increases significantly in the active phase of the disease, which can indicate disease control through the reduction of serum leptin levels, but because leptin has a positive effect on the control of infections, the use of leptin-lowering drugs can have different effects in different patients.

Due to the fact that leptin is related to body weight, one of the limitations of the present study is the lack of measurement of body mass index. Due to the higher serum leptin level in patients with systemic lupus erythematosus and its positive relationship with disease activity and inflammatory factors, leptin activity can be controlled in patients with reduced leptin. Other studies to control the effects of potential distortions, such as BMI, are also suggested.

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