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Research Article

Predictive Value of Serum Leptin in Systemic Sclerosis: A Novel Analytic Cross Sectional Study

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Abstract

Background: Systemic sclerosis (SSc) is a chronic autoimmune and multi-systematic connective tissue disease. Leptin is a cytokine like and has role in regulating immune and inflammatory response.

Objectives: To assess predictive value of serum leptin in SSc patients.

Methods: Analytic cross sectional study was performed on 40 SSc patients diagnosed according to the 1980 criteria for classification of systemic sclerosis or 2013 American College of Rheumatology/ European League against Rheumatism for the classification of systemic sclerosis criteria and compared with 40 healthy controls matched in age, sex, and body mass index. Serum leptin levels were measured using Human Leptin ELISA kit with a sandwich format.

Results: Mean serum Leptin level was significantly higher in patients compared with controls (Mean ± SEM was 10.89 ± 0.67 ng/ml Versus 6.92 ± 0.60 ng/ml, p<0.0001). Serum leptin was a valid and good test to differentiate SSc patients from healthy controls (AUC=0.80, P<0.0001). At optimum cutoff value >8.6 ng/ml the test has highest accuracy of 80% with maximum sensitivity 82.5%, and specificity 77.5% and Mathew's correlation coefficient (MCC) was 0.6. Also we can establish the diagnosis of SSc with 97.06 % confidence if the pretest probability of SSc was 90% and a negative result of the test can exclude the differential diagnosis of SSc with 97.6% confidence at 10% pretest probability.

Conclusion: Serum leptin was a valid good measure to differentiate patients with SSc from healthy controls with high accuracy, sensitivity and specificity and PPV and NPV and good MCC.

Keywords

Serum leptin; Systemic sclerosis (SSc); Leptin in SSc; Connective tissue disease

Introduction

Systemic sclerosis (SSc) is a chronic, complex disease of unknown etiology characterized by excessive fibrosis, vascular damage, and inflammation [1]. Recent studies provided strong evidence for cytokine involvement in the initiation and promotion of fibrosis. Among these cytokines, the most studied ones are transforming growth factor-a (TGF-a) connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and interleukins 1a (IL-1a), IL-4, IL-6, IL-10, IL-13 and IL-17 [2].

Leptin is a cytokine-like 16 kDa peptide produced mostly by adipose tissue and regulating food intake basal metabolism, and the b-oxidation of fatty acids [3]. It is structurally and functionally related to the IL-6 cytokine family [4]. Leptin synthesis in humans shows detectable increase as a response to acute inflammation, sepsis and secretion of inflammatory mediators such as IL-1 and TNF-a [5]. Most recent studies have focused on the potential role of leptin in modulating the immune response and leptin's inflammatory effect [6-9]. Additionally, in most inflammatory diseases, it is generally accepted that leptin displays pro-inflammatory effects (Table 1) [10].

Studies have reported that serum leptin was elevated in rheumatoid arthritis and connective tissue diseases like systemic lupus erythematous. But till now, the clinical importance of this elevation remains unknown [11,12]. In some studies, SSc patients had decreased serum leptin levels in contrast to healthy control groups [13]. Therefore, under these findings definitive conclusions cannot be drawn and because of insufficient information and very few studies related to serum leptin levels in with SSc, this study was designed to assess the predictive value of serum leptin in SSc patients.

Patients and Methods

Study design

This analytic cross sectional study was conducted by Rheumatology Unit of Baghdad Teaching Hospital-Medical City from November 2015 to April 2016. We evaluated serum leptin in SSc patients and healthy controls. Informed written consent was obtained from each participants involved in the study according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Baghdad University, College of Medicine and Medical Department.

Participants

Eligible patients included in the study were: any gender >18 years with features of systemic sclerosis diagnosed by a rheumatologist according to the criteria developed by the 1980 criteria for classification of systemic sclerosis or 2013 American College of Rheumatology/European League Against Rheumatism for the classification of systemic sclerosis [14,15]. Exclusion criteria included Patients who had overlapped features of other inflammatory arthritis or connective tissue disease or autoimmune diseases. Another group healthy individual matched in age and gender were taken as a control group.

Data entry, collection, and evaluation

We recorded demographic features of patients and controls including age, gender, and body mass index (BMI) using interviews and questionnaire. Complete blood count (CBC), urinalysis, fasting blood sugar (FBS), renal function test (blood urea, serum creatinine), antinuclear antibody (ANA), anti-scleroderma 70 (AntiScl70), anti-centromere antibody, anti-Sjögren's-syndrome-related antigen A (Anti-Ro) and anti-Sjögren's-syndrome-related antigen B (Anti-La

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antibody), thyroid function tests(T3, T4 and TSH) when appropriate were measured

Five milliliters of venous blood were drawn from peripheral veins using disposable needles and syringes from each patient and control, the blood samples then allowed to clot at room temperature in plain tubes for 30-45 min. Sera were obtained then by centrifugation of these tubes at (3000 rpm) for 10 min and kept frozen in plastic plain tubes at deep freeze temperature (-60°C).

Serum leptin levels in both groups were determined using blood samples taken in the morning after 12 h of fasting and the samples were stored at –80°C. Serum leptin levels were measured using Human Leptin ELISA kit with a sandwich format.

Statistical analysis

Statistical analysis was done using SPSS software version 23 IMB. Kolmogrove-Smirnove test was used to test the normality of distribution of variables. Continuous variables with normal distribution were expressed as Mean ± SD or mean ± SEM Categorical variables were reported as numbers and percentages. Difference between normally distributed continuous variables was done using independent T-test (Student Test). The optimum cutoff value of serum leptin was calculated using receiver operating characteristics curve (ROC) with its validity parameters (sensitivity, specificity, accuracy, Mathew's correlation coefficient, positive predictive value (PPV) and negative predictive value (NPV). P value <0.05 was considered statistically significant.

Results

A total of 80 individuals were involved in the study. Of those 40 were SSc patients and 40 controls. The mean age of patients was 35.53 ± 4.47 years and for controls was 34.83 ± 3.48 years. All of patients and controls were females. The mean BMI for patients was 17.24 ± 1.66 kg/m^2 and for controls 17.6 ± 1.69 kg/m^2. No statistical significant difference between patients and controls in demographic features (p>0.05) (Figure 1).

Serum Leptin level was significantly higher in patients compared to controls (Mean ± SEM was 10.89 ± 0.67 ng/ml Versus 6.92 ± 0.60 ng/ml, p<0.0001).

Figure 2 shows ROC curve and validity parameters of serum leptin to differentiate SSc patients from controls. Serum leptin was a valid and good test to discriminate patients from controls (AUC=0.80, P<0.0001). At optimum cutoff value >8.6 ng/ml the test had highest accuracy of 80% with maxim sensitivity 82.5%, and specificity 77.5% and Mathews correlation coefficient was 0.6. Also we can establish the diagnosis of SSc with 97.06% confidence if the pretest probability of SSc on clinical suspicion and other test was 90%. Also a negative result of the test can exclude the differential diagnosis of SSc with 97.6% confidence if the clinical setting in which the differential diagnosis of SSc was considered to be of very low probability (10% pretest probability).

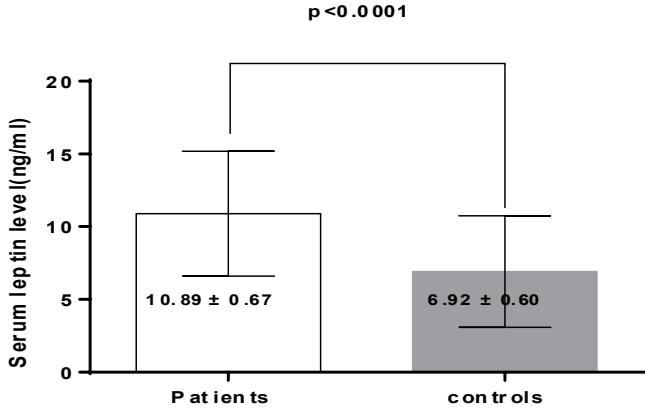

Figure 1: Comparison between serum leptin level in patients and controls.

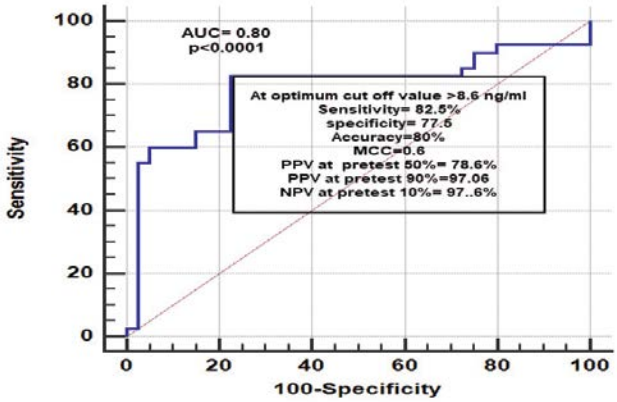

Figure 2: ROC curve with validity parameters to differentiate patients from controls.

Table 1: Demographic distribution of systemic sclerosis patients and controls.

Variables	Patients	Controls	P
Age,(mean ± SD) years	35.53 ± 4.47	34.83 ± 3.48	0.36
Female's n (%)	40 (40%)	40 (40%)	0.82
BMI mean ± SD) , kg/m²	17.24 ± 1.66	17.6 ± 1.69	0.97

[Note: BMI, body mass index. P<0.05 is not significant]

Discussion

This study evaluated serum leptin level in patients with SSc and showed that serum leptin level was significantly higher in patients compared with healthy controls. And it was a good valid test to differentiated SSc patients from controls with high accuracy, good Mathew's correlation coefficient, high sensitivity and specificity, and very high PPV and NPV. This is clinically important and may indicate that serum leptin may be used as a predictive biomarker to differentiate patients from healthy individuals.

The high serum leptin in SSc patients may be related to the fact that in SSc there is inflammation, autoimmune attack, and vasculopathy. Leptin synthesis increase in response to the inflammatory disorders and it is well-established that leptin is involved in the regulation of the inflammatory response and angiogenesis, and it has been further theorized that leptin has a role as an inflammatory marker that is to respond specifically to adipose-derived inflammatory cytokines [16-18].

In the literature, similar findings were reported by Riccieri et al. [19] who detected a significant increase of serum leptin level in the SSc patients compared to normal control patients. Also Pehlivan et al. [20] showed higher serum leptin levels in patients with SSc than the control group. However in these studies they did not assess validity of serum leptin in differentiation patients with SSc from the healthy controls.

In contrast to our study Kotulska et al. [13] found lower serum leptin levels in the SSc group than in the control group. Similarly, Budulgan et al. [21] observed lower serum leptin levels in the patient group than in the control group, although it did not reach the significant levels. The reason of conflicting studies can be explained by the heterogeneity of SSc, different stages of disease, and ethnical differences.

The main limitation of the current study is the small size of the sample for study. Another limitation worthy of mentioning is the lack of comparison between SSc patients and controls with disease. However, this can be solved by a future study with a larger sample size with controls with disease. In spite of that, this study is the first study that assessed predictive value of serum leptin and its validity in SSc to discriminate it from healthy controls [21].

In conclusion, serum leptin level was a good valid test to differentiate SSc patients from healthy controls with high accuracy and very PPV and NPV. This may indicate that serum leptin level can help in prediction and diagnosis of SSc.

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