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ORIGINAL ARTICLE

The relationship of serum leptin levels with disease activity in Egyptian patients with rheumatoid arthritis

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KEYWORDS

Rheumatoid arthritis;
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Abstract *Aim of the work:* To investigate whether serum leptin levels are elevated in patients with rheumatoid arthritis (RA) and whether these levels correlate with disease activity.

Patients and methods: A case-control study was made on 37 patients with RA and 34 healthy control subjects. The following values were assessed for each patient: erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF), swollen and tender joint counts, disease activity score 28 (DAS28), health assessment questionnaire score (HAQ), visual analog scale (VAS) of pain and serum leptin concentrations.

Results: Patients with RA had mild to moderate (DAS28 < 5.1) disease activity. The mean serum leptin in patients with RA (12.15 ± 11.48 ng/mL) was significantly higher ($p < 0.001$) than controls (3.99 ± 1.84 ng/mL). Serum leptin levels were significantly ($p < 0.001$) higher in female RA patients than in female controls. A nonsignificant difference ($p = 0.41$) was found between male patients with RA and male controls. Serum leptin levels were significantly ($p < 0.001$) higher in women than in men in both patients and controls. Serum leptin levels did not show correlation

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with age, disease duration, duration of morning stiffness, VAS, number of swollen and tender joints, DAS28, HAQ, ESR or CRP in patients with RA. Serum leptin levels were correlated positively with BMI in RA patients. The BMI was significantly higher ($p < 0.001$) in female than in male patients with RA.

Conclusion: Although leptin levels were higher in RA patients, there was no correlation with disease activity parameters, therefore, leptin levels cannot be used to reflect disease activity.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that is characterized by symmetrical synovitis, progressive joint damage, pain, fatigue, and disability. Although the exact cause of this disease is still unknown, investigation of its pathogenesis has confirmed the role of various pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) [1–3]. Accordingly, inhibition of these cytokines has become the new therapeutic strategy for RA. Recent studies have demonstrated that cytokines secreted by adipocytes (adipokines) have an important physiological role. Adipokines, including resistin, leptin and adiponectin have been demonstrated to influence eating behavior and the energy balance, and have also been noted as new mediators of the inflammatory process [4,5].

The increase in leptin production that occurs during infection and inflammation strongly suggests that leptin is a part of the cytokine network which governs the inflammatory immune response and the host defense mechanisms. Leptin plays an important role in inflammatory processes involving T-cells and has been reported to modulate T-helper cell activity in the cellular immune response [6]. It is well known that leptin has a dual role in inflammation. Leptin activates monocyte/macrophage cells and potentiates production of the pro-inflammatory cytokines, TNF-α, IL-6 and directs T-cell differentiation to Th1 phenotype, expressing interferon γ and IL-2 [7]. It also expresses certain anti-inflammatory substances by releasing IL-1 receptor antagonist [8]. Several studies have implicated leptin in the pathogenesis of autoimmune inflammatory conditions, such as experimental autoimmune encephalomyelitis, type 1 diabetes, RA, and intestinal inflammation [9–12]. The role of leptin in the modulation of immune response and inflammation has become increasingly evident [6]. It has been suggested that leptin may influence the outcome of RA [12].

The aim of this study was to assess the serum leptin levels and their relationship with disease activity parameters in Egyptian patients with RA.

2. Patients and methods

This case control study was conducted on RA patients attending the outpatient clinic of Rheumatology and Rehabilitation Department, Sohag University Hospital, in the period between May 2011 and September 2011. Thirty-seven patients (female/male = 26/11) fulfilling the American College of Rheumatology (ACR) criteria for a diagnosis of RA [13] with a mean age of 45.95 ± 12.20 years were studied. Thirty-four control subjects (female/male = 21/13) with no inflammatory disease were chosen from our outpatient clinic. The mean age of the control subjects was 47.73 ± 12.84 years. Informed consent was obtained from patients and controls participating in the study. Age, sex, disease duration, body mass index (BMI) (kg/m^2) and swollen and tender joint counts of the RA patients were recorded. Duration of morning stiffness, visual analog scale of pain (VAS) [14], disease activity index 28 (DAS28) [15], health assessment questionnaire (HAQ) [16,17], erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were used to assess disease activity. Disease activity index 28 (DAS28) is a validated index of RA disease activity. It consists of four measures: 28 tender (TJC28) and swollen joint counts (SJC28), ESR, and the patient's general health (GH) measured on a 100 mm visual analog scale. Patients were grouped according to DAS28 scores as having high (DAS28 > 5.1) or mild to moderate (DAS28 < 5.1) disease activity.

2.1. Laboratory investigations

Serum RF and CRP concentrations were determined by immuno-nephelometry methods on a Turbox nephelometer (Orion Diagnostica, Finland). The concentrations were expressed as IU/mL for RF and mg/l for CRP. RF concentration ⩾25 IU/mL and CRP concentration ⩾6 mg/l were considered positive for RF and CRP respectively. The ESR was measured by the Westergren method.

2.2. Determination of leptin levels

Venous blood samples were collected from every subject by sterile veni-puncture on the same day of history taking and clinical examination. Separated serum was kept frozen at −80 °C till the time of estimation of serum leptin. Kits used for determination were (DIA source Immuno-Assay S.A-Belgium). The DIA-source leptin ELISA is a solid phase enzyme amplified sensitivity immunoassay performed on microtiterplate. The assay uses monoclonal antibodies (MAbs) directed against distinct epitopes of human leptin. Calibrators, quality controls and samples react with the capture monoclonal antibody (MAb2) labeled with horseradish peroxidase (HRP). After an incubation period allowing the formation of a sandwich: coated MAb1–human leptin–MAb2–HRP, the microtiterplate is washed to remove the unbound enzyme labeled antibody. Bound enzyme-labeled antibody is measured through a chromatographic reaction. Chromatographic solution (TMB ready for use) is added and incubated. The reaction is stopped with the addition of stop solution and the microtiterplate is then read at the appropriate wavelength. The amount of substrate turnover is determined colorimetrically by

Table 1 Demographic and clinical characteristics of rheumatoid arthritis (RA) patients and control.

Characteristics (mean ± SD)	RA patients (37)	Control (34)	*p* value
Age (years)	45.95 ± 12.20	47.73 ± 12.84	0.532
Sex (F/M)	26/11	21/13	0.449
Disease duration (years)	3.57 ± 1.59	–	
Rheumatoid factor (%)	28 (75.7%)	–	
Morning stiffness (min)	17.84 ± 8.04	–	
VAS (0–10)	3.62 ± 1.40	–	
Number of swollen joints	1.32 ± 1.16	–	
Number of tender joints	2.89 ± 2.08	–	
DAS28 score	3.59 ± 0.66	–	
HAQ score	10.49 ± 4.15	–	
ESR (mm/1st hr)	32.19 ± 12.30	–	
CRP (mg/l)	10.65 ± 8.59	–	
Body mass index (BMI)	25.81 ± 4.97	25.85 ± 1.62	0.963
Serum leptin (ng/mL)	12.15 ± 11.48	3.99 ± 1.84	0.001*

RF: rheumatoid factor; MS: morning stiffness; VAS: visual analog scale of pain; DAS28: disease activity for 28 joint indices score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index.
* = Highly significant.

Table 2 Serum leptin levels in patients with RA and in controls according to the gender.

ng/mL	RA patients (37)	Control (34)	*p* value
Females	16.08 ± 11.62	4.92 ± 1.60	< 0.001*
Males	2.84 ± 0.99	2.48 ± 1.03	0.41
Total	12.15 ± 11.48	3.99 ± 1.84	< 0.001*

* = High significant correlation.

measuring the absorbance, which is proportional to the leptin concentration. A calibration curve is plotted and leptin concentration in samples is determined by interpolation from the calibration curve [18].

The results were analyzed by IBM-SPSS (version 19). Results were given as means and standard deviation. Student's *t*-test for continuous variables was used to examine the significance of differences between RA and control groups. *p*-value less than 0.05 was regarded as significant. The correlation between leptin levels and age, disease duration, duration of morning stiffness, swollen and tender joint counts, VAS, DAS28, HAQ, ESR, CRP and BMI was analyzed by Pearson correlation analyses.

3. Results

Age, sex and BMI did not show statistically significant differences between RA patients and control subjects ($p > 0.05$). Patients with RA had mild to moderate (DAS28 < 5.1) disease activity. The demographic and clinical characteristics of patients with RA and of control subjects are shown in Table 1.

The mean serum leptin in patients with RA (12.15 ± 11.48 ng/mL) was significantly higher ($p < 0.001$) than controls (3.99 ± 1.84 ng/mL). The mean serum leptin was significantly ($p < 0.001$) higher in female RA patients (16.08 ± 11.62 ng/mL) than in female controls (4.92 ± 1.60 ng/mL). A nonsignificant difference (p 0.41) was found between male patients with RA (2.84 ± 0.99 ng/mL) and male controls (2.48 ± 1.03 ng/mL). The mean serum lep-

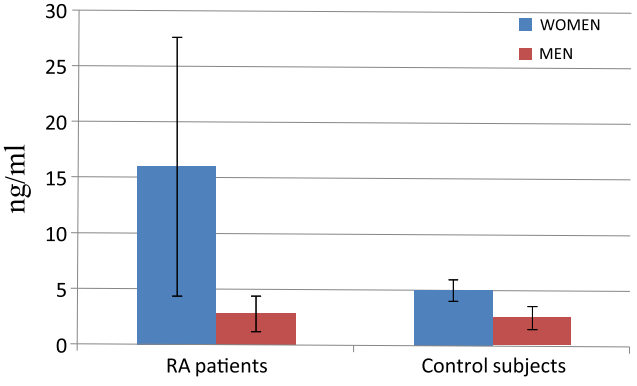

Figure 1 Serum leptin levels in patients with RA and in controls.

Table 3 Correlations between serum leptin levels and patients' characteristics.

Patient characteristics	Serum leptin	
	r	*p*
Age	0.08	0.64
Disease Duration	−0.04	0.83
MS	−0.31	0.06
VAS	−0.18	0.28
No. of swollen joints	−0.11	0.52
No. of tender joints	−0.15	0.37
DAS28	−0.02	0.89
HAQ	−0.28	0.09
ESR	0.05	0.77
CRP	−0.22	0.19
BMI	0.89	< 0.001*

MS: morning stiffness; VAS: visual analog scale of pain; DAS28: disease activity for 28 joint indices score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index.
* = High significant correlation. Values were calculated using Pearson's correlation coefficient.

Table 4 Comparison of patients' characteristics and parameters of disease activity between male and female RA patients.

Characteristics (mean ± SD)	Males (11)	Females (26)	*p* value
Serum leptin (ng/mL)	2.84 ± 0.99	16.08 ± 11.62	<0.001*
Age (years)	46.36 ± 16.5	45.77 ± 10.25	0.89
Disease duration (years)	4.09 ± 1.45	3.35 ± 1.62	0.197
Rheumatoid factor positivity (no)	8	20	0.79
Morning stiffness (min)	20.91 ± 8	16.54 ± 7.84	0.13
VAS (0–10)	3.73 ± 1.1	3.58 ± 1.53	0.77
Number of swollen joints	1.45 ± 1.29	1.27 ± 1.12	0.66
Number of tender joints	3.36 ± 2.29	2.69 ± 1.99	0.38
DAS28 score	3.58 ± 0.49	3.59 ± 0.72	0.97
HAQ score	12.09 ± 4.39	9.81 ± 3.93	0.13
ESR (mm/1st hour)	28.27 ± 8.16	33.85 ± 13.48	0.21
CRP (mg/l)	12.18 ± 10.13	10 ± 7.98	0.49
Body mass index (BMI)	20.64 ± 1.36	28 ± 4.25	<0.001*

RF: rheumatoid factor; MS: morning stiffness; VAS: visual analog scale of pain; DAS28: disease activity for 28 joint indices score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index.
* = High significant correlation.

tin was significantly ($p < 0.001$) higher in women than in men in both patients and controls (Table 2 and Fig. 1).

Serum leptin levels did not show correlation with age, disease duration, duration of morning stiffness, VAS, number of swollen and tender joints, DAS28, HAQ, ESR or CRP in patients with RA. Serum leptin levels were correlated positively with BMI in RA patients ($r = 0.89$, $p < 0.001$) (Table 3).

Patients' characteristics and parameters of disease activity did not show statistically significant differences between male and female patients with RA ($p > 0.05$). The body mass index was significantly higher ($p < 0.001$) in female than in male patients with RA (Table 4).

4. Discussion

The role of leptin in human rheumatic diseases became the subject of various studies [19]. Leptin likely plays a major role in the pathogenesis of RA. In RA patients, it was reported that fasting led to an improvement of different clinical and biologic measures of disease activity, which was associated with a marked decrease in serum leptin and a shift toward Th_2 cytokine production [20]. These features, resembling those previously depicted in ob/ob mice, suggest that leptin may also influence the inflammatory mechanisms of arthritis in humans through the induction of Th_1 responses [6].

In the current study, the mean serum leptin in patients with RA was significantly higher than in controls. These results are in consistent with other studies [12,19,21–26] and are contradictory with others [27–31]. The reasons for this discrepancy between our study and these studies may be related to the effects of medications used for treatment or to the differences in body mass indices of patients with RA. Rho et al. [32] suggested that the higher concentrations of leptin in patients with RA than controls can be attributed to differences in inflammation rather than BMI. Simons et al. [33] described that TNFα and IL-1β stimulate leptin production by human preadipocytes. Nonetheless, it is not obvious whether the increase of plasma leptin in RA is just an effect of weight change or it is rather a cause or a consequence of pathology in RA [34].

In this study the mean serum leptin in female patients with RA was significantly higher than in female controls while a nonsignificant difference was found between male patients with RA and male controls. Yoshino et al. [35] reported that serum leptin levels were significantly higher in male and female RA patients than in the corresponding controls. Nishiya et al. [36] found no difference in serum leptin between male and female patients with RA and the corresponding controls.

In our study the mean serum leptin was significantly higher in females than males in both patients and controls and this result is in agreement with other studies [19,37] that reported that concentrations of leptin were significantly higher in women than in men. There are studies reporting that gonadal steroids have an effect on circulating leptin levels. Testosterone inhibited the expression of this hormone, whereas it was increased by ovarian sex steroids [38] and this fact may explain higher plasma leptin levels in women than in men, even after adjustment for BMI [34,39]. Also, leptin is one of the hormones favoring the greater predisposition of women to autoimmune diseases [40].

In the current study, there were no correlations between serum leptin levels and age, disease duration, duration of morning stiffness, VAS, swollen and tender joint counts, DAS28, HAQ, CRP and ESR. Our results were similar to those reported in other studies [27,19,29,31,41]. In contrast, other studies [23–25,37,42] found that serum leptin level was significantly correlated with disease duration and parameters of RA activity. Serum leptin levels were higher, but did not correlate with disease activity parameters in systemic lupus erythematosus (SLE) in a study performed by Garcia-Gonzalez et al. [43]. Based on these findings in a review article, Palmer and Gabay [44] stated that leptin cannot be used to evaluate disease activity in RA and SLE patients.

In our study, serum leptin levels showed positive correlation with BMI in patients with RA [19,22,25,27,30,34,38] and women had significantly higher levels than men, as seen in previous studies [45,46]. In one study, this sex difference was reported not to be related to sex hormones or fat distribution, but possibly to differences in the hypothalamic regulation of leptin production or in adipose tissue biologic characteristics [46]. Targońska-Stepniak et al. [37] reported that the leptin concentrations corre-

lated positively with BMI only in women with RA. On the other hand, this positive correlation between serum leptin levels and BMI in patients with RA, was not found in another study [24] which suggested that regulation of leptinemia is complex and leptin levels cannot be used to assess RA activity.

In conclusion, even though serum leptin levels were found to be significantly higher in RA patients than in control subjects in this study, there was no correlation between serum leptin levels and clinical and laboratory parameters of disease activity. However serum leptin levels were positively correlated with BMI in patients with RA. In RA, circulating leptin levels do not seem to reflect disease activity.

Conflicts of interest

The authors declare no conflicts of interest.

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