Impact of obesity on functional and laboratory parameters in patients with rheumatoid arthritis

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Background
Overweight patients with rheumatoid arthritis (RA) have more disease activity, lower rates of remission, and twice as likely to require a tumor necrosis factor inhibitor. Provided that the prevalence of obesity is increasing, this may significantly affect RA incidence. An association between obesity and RA is logic, as biologic mechanisms of inflammation are present in fatty tissue, and it may be a trigger to chronic systemic inflammation. Human obesity is characterized by increased plasma leptin levels, which if elevated in morbidly obese patients may enhance constitutive immunological stimuli and increased levels of inflammatory marker.

Objectives
The aim of this study was to assess the impact of obesity and serum leptin level on disease activity and functional outcome in RA patients.

Patients and methods
This study was carried out at Minia University Hospital, Egypt. Patients were recruited from Rheumatology Outpatient Clinic from October 2012 to June 2013. It included 36 RA patients, fulfilling the 2010 ACR/EULAR classification criteria. They were divided into two groups: obese patients with a BMI of 25 or greater and nonobese patients (BMI $\leq$ 25). A total of 12 healthy individuals were included as controls. All patients were subjected to history taking and clinical examination; patient's functional status and disease activity were assessed using the Health Assessment Questionnaire (HAQ) disability index and DAS-28, respectively. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF) were determined. Serum level of leptin was measured using enzyme-linked immunosorbent assay. Data were analyzed using SPSS for Windows, version 16.0.

Results
RA obese patients showed a higher duration of morning stiffness (P = 0.02), HAQ index (P = 0.001), DAS-28 (P = 0.0001), visual analogue scale (VAS) of pain (P = 0.0001), and articular index (P = 0.001) compared with nonobese ones. They showed higher ESR (P = 0.003), serum leptin (P = 0.008), CRP (P = 0.0001), and RF (P = 0.002). There was a positive correlation between BMI and each of ESR (P = 0.003), CRP (P = 0.0001), and RF (P = 0.01). There was a positive correlation between waist circumference and each of ESR (P = 0.03), serum leptin (P = 0.03), CRP (P = 0.0001), and RF (P = 0.04). There was a positive correlation between BMI and HAQ index (P = 0.0001), DAS-28 (P = 0.001), articular index (P = 0.003), and VAS of pain (P = 0.0001). There was a positive correlation between waist circumference and HAQ index (P = 0.001), DAS-28 (P = 0.03), and VAS of pain (P = 0.0001). Moreover, there was a positive correlation between VAS of pain and serum leptin (P = 0.04). Serum leptin was correlated with CRP (P = 0.01). Linear regression analysis showed that the VAS was the first and most significant risk factor (β = 0.73; P = 0.01) and that HAQ was the second (β = –0.53; P = 0.04) to affect serum leptin levels.

Conclusion
Obese RA patients had higher disease activity parameters, clinical scores and laboratory indices, and worse functional outcomes compared with nonobese patients. Higher serum leptin levels were associated with higher disease activity scores.

Keywords:
disease activity, leptin, obesity, rheumatoid arthritis

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Introduction

Obesity is known medically as excess body fat that has accumulated to an extent that it may increase morbidity and mortality in obese individuals [1]. Obesity is most commonly caused by a combination of excessive energy intake, lack of physical activity, and genetic susceptibility – being overweight [2] primarily because of genes – as well as due to endocrine disorders, medications, or psychiatric illness. Patients with rheumatoid arthritis

(RA) have more disease activity, lower rates of remission, and are twice as likely as patients with a healthy weight to require a tumor necrosis factor inhibitor. Obesity may be considered a risk factor for developing RA. It is well known that the prevalence of obesity is increasing; consequently, this may significantly increase the incidence of RA [3]. Obesity is a controversial risk factor for RA. RA and obesity could be linked due to the presence of biologic mechanisms of inflammation in fatty tissue, which in turn can trigger systemic chronic inflammation [4]. Following a four-decade period of decline, the incidence of RA has been on the rise since 1995 [5]. The cause of this recent rise in incidence is unknown. Environmental risk factors may be responsible for increased incidence of RA recently because genetic factors do not change rapidly in populations. There are many environmental risk factors for RA, but obesity requires special attention due to recent increase in its prevalence [6]. Human obesity is characterized by increased plasma leptin concentrations. Leptin, the product of the *Ob gene* is considered to be involved in satiety regulation and obesity. Leptin is primarily released in fatty tissue [7]. It was hypothesized that leptin is involved in the induction of inflammatory state in obese individuals. The relationship between BMI, leptin, and inflammatory markers was studied and found that elevated plasma leptin concentrations in morbidly obese patients may trigger immunological stimuli, leading to increased levels of acute phase proteins and other inflammatory markers, characteristic for a chronic inflammation [8]. In RA, it was reported that fasting leads to an improvement in different clinical and biological measures of disease activity, which was associated with a marked decrease in serum leptin. These features suggest that leptin may also affect the inflammatory mechanisms of arthritis [4,9,10].

Patients and methods

Study design and patient selection

This study was carried out at Minia University Hospital, Egypt. All patients were recruited from Rheumatology Outpatient Clinic during the period from October 2012 to June 3013. It included 36 patients with established RA, fulfilling the 2010 ACR/EULAR RA classification criteria [11]. They were further divided into two groups: obese RA patients (BMI ≥25) and nonobese ones with BMI less than 25. Twelve healthy nonobese individuals were included as controls.

Ethical considerations

The nature of the present study was explained to all patients. The laboratory and radiological procedures represent standard care and pose no ethical conflicts. Verbal consent was obtained from all patients.

Study parameters

All patients were subjected to full history taking, thorough clinical examination, and laboratory investigation; patients were assessed for disease activity and severity using the Health Assessment Questionnaire (HAQ) disability index for RA [12] and for disease activity using DAS-28 activity [13]. Erythrocyte sedimentation rate (ESR) was assessed using the Westergren method [14]. C-reactive protein (CRP) was evaluated using the latex agglutination slide test for qualitative and semiquantitative determination of CRP in nondiluted serum [15]. Rheumatoid factor was determined using the latex fixation test [16].

Lipid profile

Total cholesterol, triglycerides (TAGs), and high-density lipid (HDL) cholesterol were measured. Low-density lipid (LDL) cholesterol was calculated according to the equation LDL = total cholesterol-HDL-(triglycerides÷5) [17]. Serum leptin was measured using the enzyme linked immunosorbent assay (ELISA) using Human Leptin ELISA, Clinical Range kit, provided by BioVendor Research and Diagnostic Products, *http://www.biovendor.com*.

Statistical analysis

Data were coded, entered, and analyzed using the Statistical Package for the Social Sciences (SPSS for Windows version 16.0, IBM company, Armonk, New York, United States). Two-tailed tests were used throughout, and statistical significance was set at the conventional level of less than 0.05. The following statistics were carried out. (a) *Descriptive statistics*: The range, means, and SD were calculated for interval and ordinary variables and frequencies and percentages for categorical variables. (b) *Group comparisons*: Comparisons were made using three procedures: Student's *t*-test, which was used to compare the difference between two group means for interval and ordinal variables; the χ^2-test: The χ^2-test is a nonparametric measure of the statistical independence of the categories of two variables measured on the nominal or dichotomous scale. We used the χ^2-test to test the significance of the differences between the two and three groups in categorical variables. The bivariate correlation procedure computes Pearson coefficient with its significance levels. Pearson's correlation coefficient is a measure of linear association.

Results

Demographic data

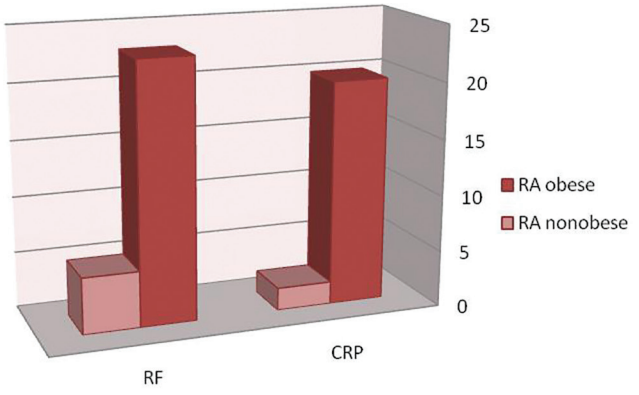
Group I included 36 RA patients, 33 women (92%) and three men (8%). Their ages ranged from 23 to 61 years, with a mean of 45.9 ± 9.4 years, and their disease duration ranged from 2 to 18 years, with a mean of 6.8 ± 3.8 years. Group II included 12 healthy individuals: 10 women (83.3%) and two men (16.7%). Their ages ranged from 22 to 41 years, with a mean of 25.4 ± 5.6 years. Obese RA patients showed statistically significantly higher morning stiffness (P = 0.02), HAQ index (P = 0.001), DAS-28 (P = 0.0001), visual analogue scale (VAS) of pain (P = 0.0001), and articular index (AI) (P = 0.001) when compared with nonobese ones (Table 1). Obese RA patients showed a statistically significantly higher ESR (P = 0.003), serum leptin (P = 0.008), CRP (P = 0.0001), rheumatoid factor (RF) (P = 0.002), and serum TAG (P = 0.03). (Table 2) (Figs 1 and 2) Serum leptin showed a statistically significantly higher level in RA patients when compared with the control group, with a P value of 0.001 (Fig. 3). Correlation studies between obesity parameters and laboratory findings in RA revealed a highly significant positive correlation between BMI and each of ESR (P = 0.003), serum TAG (P = 0.003), CRP (P = 0.0001), and RF (P = 0.01), whereas there was no statistically significant correlation between BMI and serum leptin or serum cholesterol. There was a significant positive correlation between waist circumference (WC) and each of ESR (P = 0.03), serum leptin (P = 0.03), CRP (P = 0.0001), and RF (P = 0.04) (Table 3). Correlations between obesity parameters and activity indexes in RA showed that there was a highly significant positive correlation between BMI and each of HAQ index (P = 0.0001), DAS-28 (P = 0.001), AI (P = 0.003), and VAS of pain (P = 0.0001). There was a highly significant positive correlation between WC and each of HAQ index (P = 0.001), DAS-28 (P = 0.03), and VAS of pain (P = 0.0001) (Table 4 and Fig. 4). Correlations between laboratory findings and activity indexes in RA showed that there was a highly significant positive correlation between VAS of pain and serum leptin (P = 0.04) (Fig. 5). In RA, leptin also showed a significant correlation with CRP (P = 0.01). Finally, a linear regression analysis was carried out for the different groups to identify the most significant risk factors affecting serum leptin. It was noticed that, in RA, the VAS of pain was the first and most significant risk factor (β = 0.73; P = 0.01) and HAQ index was the second significant risk factor (β = −0.53; P = 0.04) affecting serum leptin in this group, followed by AI, WC in centimeters, DAS-28, ESR first hour, serum cholesterol, serum TAG, BMI, and CRP (Tables 4 and 5).

Table 1 Comparison between functional assessment scores in rheumatoid arthritis

Functional scores	RA obese (N = 25)	RA nonobese (N = 11)	t	P value
HAQ index				
Range	9–31	4–9	3.6	0.001**
Mean ± SD	18.9 ± 5.3	12.2 ± 4.2		
DAS-28				
Range	4.2–6.2	3.7–4.7	4.25	0.0001**
Mean ± SD	5.3 ± 0.78	4.3 ± 0.38		
VAS of pain				
Range	2–7	1–3	5.7	0.0001**
Mean ± SD	3.8 ± 1.2	1.6 ± 0.67		
AI				
Range	8–30	4–13	3.6	0.001**
Mean ± SD	14.6 ± 5.1	8.5 ± 2.8		

AI, articular index; DAS-28, disease activity score 28 of RA patient; HAQ index, Health Assessment Questionnaire; RA, rheumatoid arthritis; VAS, visual analogue scale; **Highly significant at P < 0.01.

Figure 1



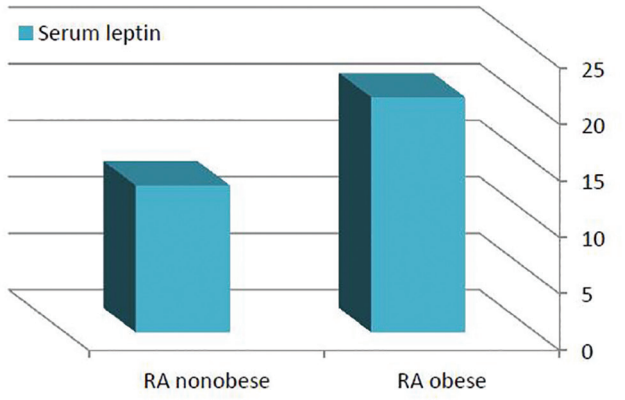
Comparison between CRP and RF in RA subgroups. CRP (P = 0.0001); RF (P = 0.002). CRP, C-reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 2 Comparison between laboratory findings in rheumatoid arthritis subgroups

Laboratory findings	RA obese (N = 25)	RA nonobese (N = 11)	χ^2/t	P value
ESR (mean ± SD)	50.4 ± 24.9	24.8 ± 10.7	3.2	0.003**
Serum CHOL (mean ± SD)	172.8 ± 44.7	166.6 ± 39.2	0.42	0.6
Serum TAG (mean ± SD)	90.5 ± 35.9	64.8 ± 17.7	2.23	0.03*
Serum leptin (median)	21.6	11.4	7.08	0.008**
CRP (mean ± (no (%))	20 (80%)	2 (18.2%)	12.2	0.0001**
RF (mean ± (no (%))	23 (92%)	5 (45.5%)	9.57	0.002**

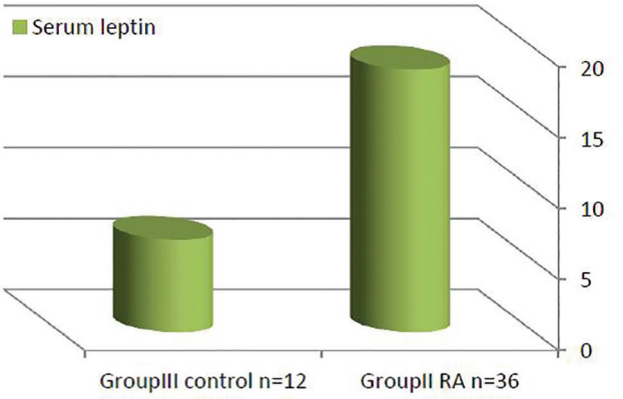
CHOL, cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; TAG, triglyceride; *Significant at P < 0.05; **Highly significant at P < 0.01.

Figure 2



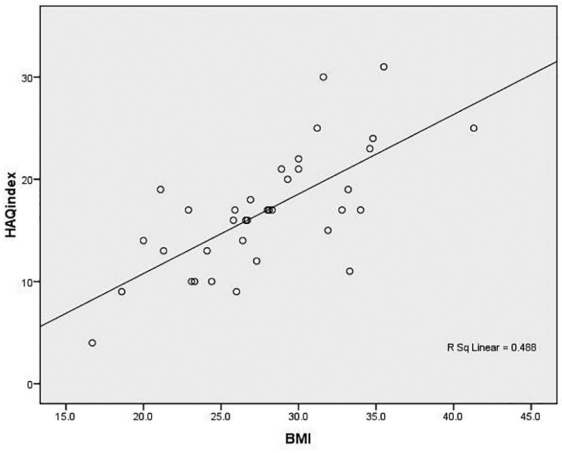
Serum leptin levels in RA subgroups. RA, rheumatoid arthritis.

Figure 3



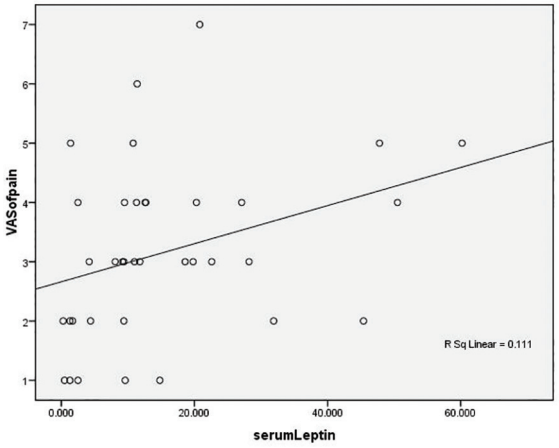
Comparison between serum leptin in RA patients and controls. RA, rheumatoid arthritis.

Figure 4



Correlation between BMI and the HAQ index in RA patients (R = 0.69, P = 0.0001). HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis

Figure 5



Correlation between VAS of pain and serum leptin in RA patients (R = 0.33, P = 0.04). RA, rheumatoid arthritis; VAS, visual analogue scale.

Discussion

Obesity is medically known as excess body fat that has accumulated to the extent that it may increase morbidity and mortality in obese individuals [1]. The mechanism by which obesity may lead to RA is unknown, but several mechanisms have been postulated. One logic mechanism is the association between obesity and chronic inflammation. The amount of fatty tissue expands during weight gain, and adipocytes produce adipocytokines and inflammatory cytokines, including adiponectin, leptin, tumor necrosis factor, interleukin-6, CRP, and others [18]. The major adipocytokines have immunomodulatory properties and impact inflammation [19]. This is an active area of research, and both adipocytokines and inflammatory cytokines are implicated in the pathophysiology of rheumatic diseases, such as RA. RA patients in the present study showed a significant difference in activity indexes in terms of HAQ index, DAS-28, VAS of pain, and AI and in inflammatory markers such as ESR, CRP, and RF. This is in agreement with the findings of Stavropoulos-Kalinoglou *et al.* [20], who studied a total of 294 RA patients and divided them into four groups on the basis of BMI (underweight, normal weight, overweight, and obese) and found that there was a significant difference in CRP, RF, and HAQ between the groups: patients who were either underweight or obese had significantly higher CRP, RF, and poorer HAQ than those who had normal weight, which means that obese RA patients have more active disease on clinical, functional, and laboratory levels. Serum leptin and serum TAG in RA patients in the present study were significantly higher in obese compared with nonobese individuals. Moreover, we found significantly higher serum leptin in RA patients compared with controls regardless of BMI. Similarly, Solus *et al.* [21]

Table 3 Correlation between obesity parameters and laboratory findings

Laboratory findings	BMI	WC
ESR first hour		
R	0.47	0.34
P value	0.003**	0.03*
Serum TAG		
R	0.35	0.19
P value	0.03*	0.24
Serum CHOL		
R	0.21	0.22
P value	0.2	0.18
Serum leptin		
R	0.28	0.35
P value	0.09	0.03*
RF		
R	0.41	0.34
P value	0.01*	0.04*
CRP		
R	0.62	0.57
P value	0.0001**	0.0001**

CHOL, cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; TAG, triglyceride; WC, waist circumference; *Significant at $P < 0.05$; **Highly significant at $P < 0.01$.

Table 4 Correlation between obesity parameters and activity indexes in rheumatoid arthritis

Laboratory findings	WC	BMI
HAQ index		
R	0.54	0.69
P value	0.001**	0.0001**
DAS-28		
R	0.35	0.51
P value	0.03*	0.001**
AI		
R	0.3	0.48
P value	0.07	0.003**
VAS of pain		
R	0.55	0.67
P value	0.0001**	0.0001**

AI, articular index; DAS, disease activity score; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; VAS, visual analogue scale; WC, waist circumference; *Significant at $P < 0.05$; **Highly significant at $P < 0.01$.

found a significant higher serum leptin level in patients with RA than in the control group with comparable BMI. Park *et al.* [22] also reported a significantly higher cholesterol and TAG in RA patients when compared with age-matched/sex-matched healthy controls; thus, serum leptin could be considered a marker of inflammation in RA. This is in agreement with the findings of Allam and Radwan [23], who reported a higher serum leptin in RA patients when compared with controls. However, in the present study all patients had late RA. Moreover, most of the patients in their study were underweight and normal weight, but in the present study most of the patients were overweight and

Table 5 The risk factors affecting serum leptin in rheumatoid arthritis

Variables	*P* value	β
VAS of pain	0.01	0.73
HAQ index	0.04	−0.53
AI	0.1	−0.41
WC (cm)	0.4	0.21
DAS-28	0.4	−0.18
ESR first hour	0.5	0.15
Serum CHOL	0.6	0.11
Serum TAG	0.7	0.093
BMI	0.7	0.090
CRP	0.7	0.07

Dependant variable is serum leptin; AI, articular index; CHOL, cholesterol; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; TAG, triglyceride; VAS, visual analogue scale; WC, waist circumference.

obese. The present study shows a positive significant correlation between obesity parameters and activity indexes in RA patients. In addition, obesity parameters in turn showed a high positive significant correlation with laboratory findings. This suggests that obesity has a significant association with the disease activity and the elevation of serum leptin and lipid profiles in RA patients. Similar to these findings, Stavropoulos-Kalinoglou *et al.* [20] reported a significant positive correlation between BMI and ESR, CRP, and HAQ in RA patients. Serum leptin and TAG in the presented study in RA patients also showed a significant positive correlation with activity indexes and inflammatory markers. This is in agreement with the findings of Solus *et al.* [21], who found that serum leptin was positively correlated with the DAS-28 and the CRP concentration. Park *et al.* [24] also investigated whether lipid profile levels correlated with RA activity in RA patients. They found that the higher the serum TAG and cholesterol levels the higher the CRP, DAS-28, and ESR and vice versa in the start and end of the study. In contrast to these findings, Allam and Radwan [23] reported that serum leptin levels did not show any correlation with age, disease duration, duration of morning stiffness, VAS, number of swollen and tender joints, DAS-28, HAQ, ESR, or CRP in patients with RA. Assuming that obesity is associated with a state of chronic mild inflammation, with raised circulating levels of inflammatory markers, they also agreed that the expression and release of inflammation-related adipokines generally rises as adipose tissue expands. This is in agreement with the current results, which showed a correlation between serum levels of leptin with inflammatory markers and with BMI [25,26]. The elevated production of inflammation-related adipokines is increasingly considered to be [27] important in the development of diseases linked to obesity.

Conclusion

Obese RA patients had higher disease activity parameters, clinical scores and laboratory indices, and worse functional outcomes compared with nonobese patients. Higher serum leptin levels were associated with higher disease activity scores.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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