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The impact of anti-TNF-α therapy on leptin and inflammatory markers in rheumatoid arthritis patients: a case-control study

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Abstract

Background and objective Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by synovial inflammation, cartilage, and bone destruction. Several studies have shown that leptin plays an important role in the pathophysiology of RA disease. This study aimed to evaluate serum levels of leptin in RA patients receiving biologic drugs compared to RA patients managed by non-biologic drugs, and healthy individuals.

Methods and material In this case-control study, three groups including RA patients receiving biological drugs (remission RA patients; $n=20$), RA patients receiving DMARDs (active RA patients; $n=20$), and healthy controls ($n=20$) were included. Serum leptin levels and inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were measured in all participants. These measurements were subsequently compared across the three groups. Also, the correlation between leptin and inflammatory markers in each group was evaluated.

Results In this study serum leptin levels in remission RA patients, active RA patients, and healthy individuals were 14.49 ± 6.73, 16.94 ± 7.72, and 7.59 ± 5.94, respectively. Serum leptin level was significantly higher in patients with RA compared to healthy controls. No significant difference was observed in serum leptin levels between the two groups of RA patients ($P<0.001$). There was a lost correlation between leptin and inflammatory markers in patients with active RA. However, a new correlation between leptin and inflammatory markers emerged in RA patients receiving biological drugs.

Conclusion Our findings suggest that anti-TNF-alpha agents do not modulate serum leptin levels in RA patients. However, these agents may change a correlation between leptin and C-reactive protein (CRP) that is absent in patients with active RA.

Trial registration Not applicable in case control study.

Keywords Rheumatoid arthritis, Leptin, Anti-TNF-alpha, Treatment

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects 0.5–1.3% of the adult population [1–3]. Women are affected 2 to 3 times more often than men. The disease is characterized by synovial inflammation, as well as the destruction of cartilage and bone [4–6]. The identification of autoantigens by the immune system leads to various inflammatory mechanisms, including the secretion of inflammatory cytokines and soluble mediators by immune cells and synovial tissues [3, 7, 8, 9]. Treatment strategies for patients with RA could include disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate; biological agents like TNF-alpha inhibitors; and targeted synthetic DMARDs such as tofacitinib [1, 10, 11].

Leptin is a type of cytokine specifically pleiotropic adipokine hormone that is predominantly secreted by adipose tissue [12]. It induces leukemia inhibitory factor, neuronal growth factor, and human growth hormone, and affects energy homeostasis and immune responses through various pathways in the endocrine system [13]. Numerous studies have shown that leptin plays an important role in the pathophysiology of RA. Several studies have reported elevated levels of *leptin hormone* in the blood serum and synovial fluid of patients with RA compared to healthy individuals. The research findings indicate higher leptin levels are correlated with the severity of the RA. This increase in leptin production during periods of infection and inflammation is driven by the elevated synthesis of inflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [14, 15].

Leptin plays a significant role in the pathophysiology of RA by affecting immune responses and causing inflammation. In this study, the researchers assessed the serum levels of leptin in RA patients who were treated with anti-TNF-alpha drugs. They compared these levels to those of RA patients treated with synthetic disease-modifying antirheumatic drugs (sDMARDs) and to healthy individuals.

Methods and material

Patient selection and population

Patients referred to the outpatient rheumatology clinic of Imam Khomeini Complex Hospital were asked to participate in our study. The sample size was determined based on the following formula with the 80% power of the study which and divided into three groups [16].

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

The case group consisted of RA patients receiving anti-TNF drugs (adalimumab) who were in remission ($n = 20$). The control group consisted of RA patients not receiving biologics with active RA receiving synthetic disease-modifying antirheumatic drugs (sDMARDs) (Methotrexate) ($n = 20$) and a healthy control group ($n = 20$). There were no significant differences in age and gender between these three groups. The control group comprised matched participants without this specific condition, taking into account age, sex, and other demographic factors.

Inclusion criteria

The patients included if they met following criteria:

1. A confirmed diagnosis of RA in case and control group based on ACR 1987 diagnostic [17] and the 2010 ACR/EULAR classification criteria by a rheumatology specialist [18].
2. Patients in the case group must be in remission phase of RA with a DAS28-ESR score of less than 2.6 is in remission [19].
3. Only patients who are fully informed about the study process and who sign an informed consent form will be included in the study.
4. Receipt of at least one biological agent for patients in the case group.
5. Absence of any autoimmune diseases, cancer, infections, or allergies in healthy control individuals.
6. The control group consisted age and sex-matched individuals without any history of autoimmune diseases, allergies, or chronic infections who were referred to the same center for evaluation of non-inflammatory conditions as confirmed by medical history and clinical evaluation.
7. Absence of obesity in individuals across all three groups.

Exclusion criteria for patients

The patients excluded if they met following criteria:

1. Patient's withdrawal of consent to continue participation in the study.
2. Use of any immunosuppressive medications within three months prior to the study in both patient and healthy control groups.
3. Diagnosis of any other autoimmune diseases.

Study procedures

The careful selection process aimed to create a uniform study population, facilitating a more accurate assessment of the risk factors linked to the condition. Because the patients were referred to the rheumatology clinic; therefore, collecting any clinical information related to the patients' health was possible.

A questionnaire was completed for all study participants. This questionnaire consisted of demographic and clinical information. Demographic information includes age, gender, and BMI. Clinical symptoms include extra-articular symptoms, disease severity, number of swollen joints, and number of tender joints, as well as laboratory findings including CRP and ESR. Peripheral blood samples were obtained from all participants. The samples were centrifuged for analysis, and the supernatant was removed and frozen at -80 C until further analysis. The leptin levels were measured in serum samples. All blood sample processing procedures were carried out by trained research staff.

Determination of leptin levels

All assays were performed in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit for leptin (R&D system, USA), following the manufacturer's instructions. The ELISA kit had a lower detection limit of 10 pg/ml for leptin. For leptin levels below the detection limit, a concentration of 50% of the detection limit was used for statistical analysis.

Statistical analysis

In this study, we used the IBM SPSS v.25 software (SPSS Inc, Chicago, IL) for statistical analysis. The normal distribution of the numerical variables for subjects and controls was assessed using Kolmogorov-Smirnov Z-test. A one-way analysis of variance (ANOVA) was conducted to compare serum leptin levels across three groups: healthy controls, rheumatoid arthritis (RA) patients in remission, and RA patients with active disease. Categorical variables were compared by $\chi 2$ test. Pearson correlation test was utilized to evaluate the relationship between leptin and inflammatory markers including CRP and ESR. The P-value less than 0.05 was considered statistically significant.

In the statistical analysis phase, a multiple linear regression was executed to investigate the effects of patient group, sex, weight, CRP, and ESR on leptin levels while adjusting for potential confounders. Leptin was specified as the dependent variable, and all predictors were included simultaneously in the model. Multicollinearity was assessed using tolerance and variance inflation factor (VIF) values, and residuals were examined to ensure normality and homoscedasticity. The significance level was set at $p < 0.05$, and results were interpreted using unstandardized coefficients, 95% confidence intervals, and model fit statistics (R^2 and adjusted R^2). This approach allowed for the evaluation of the independent contributions of each predictor to leptin levels while controlling for the effects of other variables in the model.

Ethical consideration

Informed consent was obtained from all participants and the study protocol was approved by the ethics committee of Tehran University of Medical Sciences (No: IR.TUMS.IKHC.REC.1398.128). It is imperative to note that the participation of the patient or their parents is entirely voluntary. If they are unwilling to cooperate, they will not be included in the study. Moreover, the patient's information will remain strictly confidential, and there is no obligation to provide personal details on the questionnaire.

Results

The baseline demographic and clinical characteristics of the study participants are summarized in Table 1. The three groups - patients with RA in remission receiving adalimumab, patients with active RA receiving synthetic disease-modifying antirheumatic drugs (sDMARDs), and healthy controls - were well-matched in terms of sex, height, weight, and body mass index (BMI), with no statistically significant differences observed between the groups (all $p > 0.05$). The mean serum leptin levels differed significantly among the three groups ($p < 0.001$). The mean serum levels of leptin in patients with remission RA receiving adalimumab, active RA patients receiving sDMARDs, and healthy individuals were 14.49 ± 6.73, 16.94 ± 7.72, and 7.59 ± 5.94, respectively.

A one-way ANOVA was conducted to compare serum leptin levels across three groups; healthy controls, RA patients in remission, and RA patients with active disease. The assumption of homogeneity of variances was met (Levene's test, $p = 0.618$). There was a statistically significant difference in mean leptin levels between the groups ($F(2, 57) = 10.048$, $\eta^2 = 0.26$, $p < 0.001$). Analysis test revealed that leptin levels were significantly

Table 1 Baseline demographic and laboratory characteristics of the participants

Variable	Healthy	Groups RA. Flare	RA. Remission	*P* value
Sex (Male/Female)	10/10	11/9	9/11	0.81
Age	35 ± 8.5	36 ± 7.43	38 ± 5.5	0.25
Height (cm)	163 ± 6.51	168 ± 5.65	164 ± 7.59	0.17
Weight (kg)	72.95 ± 10.83	72.05 ± 8.41	67.63 ± 14.03	0.29
BMI (kg/m^2)	27.34 ± 3.57	25.79 ± 2.56	25.08 ± 3.94	0.11
Leptin (ng/ml)	7.59 ± 5.94	16.94 ± 7.72	14.49 ± 6.73	< 0.001
CRP (mg/l)	2.25 ± 2.4	38.95 ± 22.86	4.99 ± 2.21	< 0.001
ESR (mm/hr)	9.7 ± 2.65	43.35 ± 23.19	13.75 ± 3.41	< 0.001
RF	-	Positive:17 Negative: 3	Positive: 16 Negative:4	0.5
Anti-CCP	-	Positive:19 Negative: 1	Positive:18 Negative: 2	0.5

Data are presented as Mean ± SD, Categorical variables are compared by $\chi 2$ test. The rest of the variables are compared by ANOVA-test. BMI, body mass index, RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptides; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

higher in both the RA Remission group (mean difference = 6.895, $p = 0.006$) and the RA Flare group (mean difference = 9.350, $p < 0.001$) compared to healthy controls. However, there was no significant difference in leptin levels between the RA Remission and RA Flare groups (mean difference = -2.455, $p = 0.497$). These findings suggest that leptin levels are elevated in RA patients regardless of disease activity status ($P < 0.001$, Fig. 1).

Serum CRP and ESR concentrations were also compared between the 3 groups. Since the distribution of CRP and ESR data was normal, a one-way analysis of variance (ANOVA) was used to compare the mean serum CRP and ESR concentrations between the three groups. Tukey's post-hoc test was then used to determine the specific pairwise differences between the groups. The mean levels of ESR and CRP were significantly higher in active RA patients than in RA patients in remission, and healthy controls. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies were positive in 16 and 18 cases of the remission RA group and in 17 and 19 cases of the active RA group, respectively.

The results of the Pearson correlation analysis are presented in Table 2; Fig. 2. In the healthy control group, leptin levels were found to be significantly and positively correlated with both CRP levels ($r = 0.502$, $p = 0.01$) and ESR ($r = 0.384$, $p = 0.04$). However, this significant correlation between leptin and inflammatory markers was not observed in the group of patients with active RA flare ($p > 0.05$ for both CRP and ESR).

In the group of patients with rheumatoid arthritis (RA) in remission who were receiving biological treatment, leptin levels exhibited a significant negative correlation with both C-reactive protein (CRP) (r = -0.454, $p = 0.02$) and erythrocyte sedimentation rate (ESR) (r = -0.469, $p = 0.02$). Table 2 presents the Pearson correlation analyses examining the relationships between leptin and inflammatory markers in the different study groups. Importantly, these inverse associations between leptin and the inflammatory markers CRP and ESR remained statistically significant even after controlling for the participants' gender in the analysis.

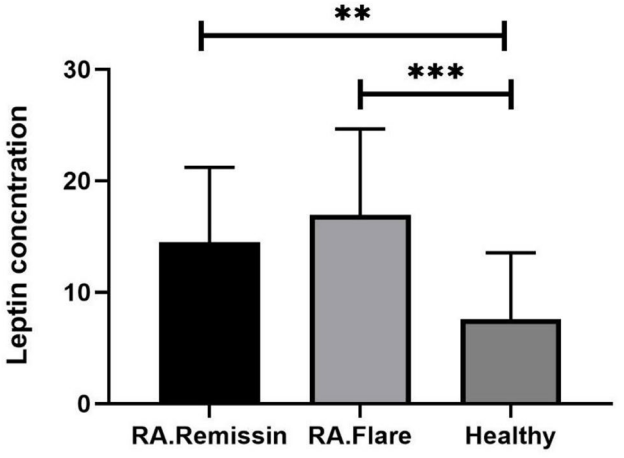

Fig. 1 Comparison of the mean serum levels of leptin between three groups of the study using ANOVA test (** P value < 0.01; *** P value < 0.001)

Table 2 Correlation between leptin and inflammatory markers

Variables	Leptin		
	Healthy	**RA flare**	**RA remission**
CRP	$r = 0.502$, $P = 0.01$*	$r = 0.217$, $p = 0.17$	r= -0.454, $p = 0.02$*
ESR	$r = 0.384$, $p = 0.04$*	$r = 0.011$, $p = 0.48$	r= -0.469, $p = 0.02$*

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; r, Pearson correlation coefficient; *P*: *p* value;

Multiple linear regression to adjust confounders

The multiple linear regression analysis conducted to predict leptin levels while adjusting for potential confounders including age, sex, weight, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) reveals significant insights. The model summary indicates a moderate correlation ($R = 0.540$) and explains approximately 29.2% of the variance in leptin levels (R^2 = 0.292) with a statistically significant F-change ($F(4, 54) = 5.570$, $p < 0.001$). This suggests that the selected predictors collectively

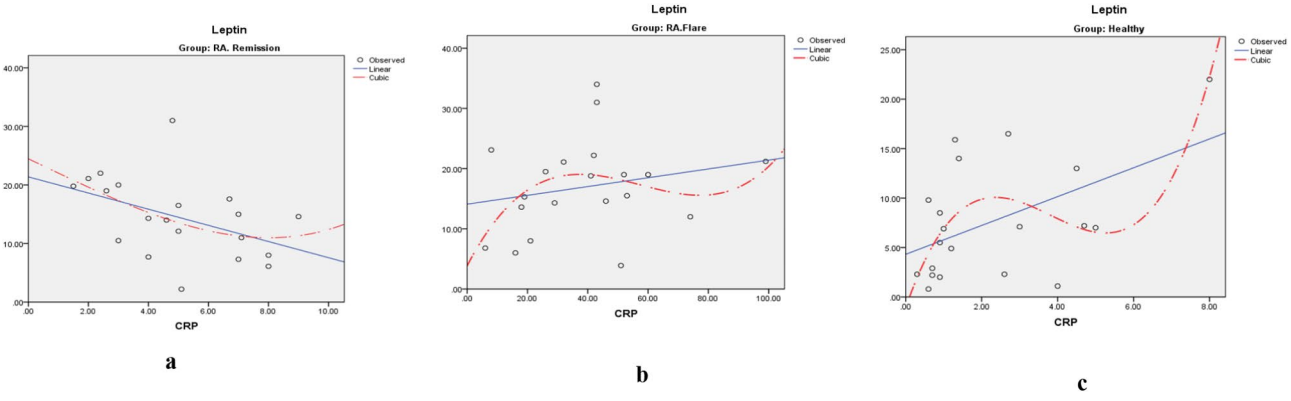

Fig. 2 Correlation between leptin and CRP in (**a**) RA remission groups, (**b**) RA flare up groups, (**c**) healthy groups

contribute to understanding leptin variability, emphasizing the importance of controlling for confounding variables in epidemiological studies.

In this multiple linear regression analysis, patient group was examined as the primary predictor of leptin levels while adjusting for confounders such as age, sex and weight. The model explained approximately 40.4% of the variance in leptin levels ($R^2 = 0.404$) and was statistically significant ($F = 7.181$, $p < 0.001$). After adjusting for age, sex, weight, CRP, and ESR, patient group emerged as a significant predictor of leptin levels ($p < 0.05$), with the 95% confidence interval for the group coefficient ranging from −5.351 to -1.190, indicating significant differences in leptin levels between the groups.

However, among predictors sex was another variable with a statistically significant effect on leptin levels (95% CI: 2.073, 9.311; $p < 0.05$). This result indicates that leptin levels were significantly higher in females compared to males. In contrast, age, CRP, weight, and ESR did not have statistically significant effects on leptin levels, as their 95% confidence intervals included zero. The absence of multicollinearity between predictors was confirmed by tolerance values greater than 0.504 and variance inflation factor (VIF) values. Residual diagnostics, including a mean residual of 0.000 and a residual standard deviation of 6.590, indicated that the model was unbiased and that the assumptions of linear regression were adequately met. These results suggest that leptin levels vary significantly across patient groups even after accounting for age, sex and weight, highlighting the importance of group classification in understanding leptin variability.

Discussion

The primary objective of this study was to evaluate serum leptin levels in patients with RA who were in remission and undergoing anti-TNF therapy, compared to both patients with active RA receiving conventional synthetic DMARDs and healthy controls. Leptin, a hormone with dual roles as an anti-obesity agent and an immune response regulator, plays a critical role in mediating metabolic regulation and immune function [20–22]. It influences the secretion of acute-phase reactants, including interleukin-1 and TNF-α. Leptin serves as a link between nutritional status and immune response, with reduced plasma leptin levels associated with impaired immune function [21, 23]. Elevated blood leptin levels, often observed in obesity, increase susceptibility to cardiovascular disease, autoimmunity, and cancer [24, 25].

Our study found that anti-TNF therapy does not alter leptin levels in RA patients. However, this therapy did disrupt the previously observed correlation between leptin and inflammatory markers such as CRP and ESR in these patients. Consistent with our findings, Gonzalez-Gay et al. [26], reported that anti-TNF-alpha therapy (adalimumab) does not affect leptin levels in patients with severe RA, suggesting that the therapeutic benefits are not modulate through leptin modulation. This is also supported by Härle et al. [27] who found that adalimumab does not influence leptin or adiponectin levels in RA patients. Furthermore, Popa et al. [28] assessed leptin levels in 58 RA patients at baseline, 2 weeks, and 6 months after initiating anti-TNF therapy, which aligns with our observation of no significant change in leptin levels over time.

They found that anti-TNF agents have a limited influence on serum leptin concentrations. Derdemezis et al. [29] also reported that leptin and adiponectin serum concentrations did not change significantly after 6-month treatment with infliximab. The published evidences confirm our findings regarding the lack of significant difference in serum levels of leptin between RA patients who were under treatment with anti-TNF drugs and those receiving non-biologic drugs. However, in contrast to our findings, a study conducted by Kopec-Medrek et al. [30] revealed elevated serum concentrations of leptin in RA patients after one year of treatment with infliximab. This discrepancy may be partly due to differences in the study groups between Kopec-Medrek et al.'s study [30] and the present study.

In other autoimmune diseases such as psoriasis and ankylosing spondylitis, serum levels of leptin do not show significant alteration during the treatment with infliximab [31, 32]. Therefore, it seems that anti-TNF-alpha therapy does not modulate serum concentrations of leptin in RA patients, and the beneficial effects of these agents are mediated independently of any reduction in serum levels of leptin.

The current findings of this study are consistent with the results of our previous research [33] which demonstrated a positive association between leptin and CRP levels in healthy individuals. However, this correlation was found to be lost in the group of RA patients experiencing disease flare. The novel and key finding from the present study is the identification of a new negative correlation between leptin and inflammatory markers, including CRP and ESR in RA patients who were receiving anti-TNF-alpha therapy. This contrasts with the positive relationship typically observed in healthy controls and the lack of correlation seen in the RA flare group.

Though the findings of this study could provide new insights for rheumatologists and internists, the present study has several important limitations that should be acknowledged. The primary limitation is the relatively small sample size, which may limit the statistical power and generalizability of the findings. This issue arises from various factors, including patients' satisfaction to continue treatment and participate in the study, loss to follow-up rates, and the high costs associated with such

research. However, further studies involving larger populations and long-term follow-up are needed to confirm the findings of the current study. Additionally, the cross-sectional nature of the data collection is a limitation, as it precludes any analysis of longitudinal trends or causal relationships between the variables of interest. The current analysis is largely limited to univariable and bivariable statistical comparisons, which may oversimplify the complex relationships between the factors under investigation. Future research with larger, more comprehensive datasets and longitudinal designs would be valuable to build upon the preliminary findings reported here and provide a more robust understanding of the associations between the variables of interest.

Conclusion

Based on the findings of the current study and the existing literature, it can be concluded that anti-TNF-alpha inhibitors do not seem to modulate serum concentrations of leptin. However, they may change the previously observed correlation between leptin and inflammatory markers including CRP and ESR in patients with RA.

Abbreviations

ESR	Erythrocyte Sedimentation Rate
CRP	C-Reactive Protein
RA	Rheumatoid arthritis
DMARDs	Disease-modifying antirheumatic drugs
DAS28	Disease Activity Score 28
TNF	Tumor Necrosis Factor
Anti-TNF	Anti-tumor necrosis factor-alpha

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Author contributions

MK, SR. N. made contributions to conception and design of the study; SR.N, MK, MN, and SR. made contributions to the acquisition of the data and patient management; SR.N. and M.K. made contributions to the administrative work; SR.N, MK, SR. and MN performed the statistical analysis. All authors were involved in the interpretation of results and drafted the manuscript which was revised by SR.N, and MG. Critical revision of the final article for important intellectual content was done by SR.N, MK, and MG. All authors have read and approved the final manuscript.

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Data availability

The datasets during the current study are not publicly available due to the human research approval received but are available (anonymyzed) from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Tehran University of Medical Sciences with NO IR.TUMS.IKHC.REC.1398.128. Written informed consent was obtained from all participants prior to enrollment. The study adhered to the principles outlined in the Declaration of Helsinki.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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