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Plasma Leptin Does Not Reflect the Effect of High Body Mass Index on Disease Activity in Rheumatoid Arthritis

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ABSTRACT

Background: The effect of obesity on disease severity in rheumatoid arthritis (RA) remains controversial. Adipocytes secrete pro-inflammatory cytokines and adipokines which may contribute to RA disease activity. The goal of the present study is to address the association between body mass index (BMI) with plasma levels of leptin, pro-inflammatory cytokines, and RA disease severity.

Methods: Fifty RA patients (20 newly diagnosed and 30 under treatment) as well as 30 age- and sex-matched healthy subjects were included in this survey. The plasma levels of leptin and pro-inflammatory cytokines, including TNF-α and IL-6, were measured, and the results were compared among the patients in the three different categories of BMI, including <25, ≥25–30, and ≥30.

Results: In our study, a significant positive correlation was observed between disease activity score-28 (DAS-28) and BMI in overweight (OW) RA patients (p = .036 r = 0.440). The plasma levels of leptin were significantly higher in patients group, compared to healthy subjects (p < .05); moreover, leptin levels were significantly higher in OW and obese patients compared to RA patients with normal BMI (p = .011, p = .001, respectively) and also BMI had positive correlation with leptin concentrations just in the newly diagnosed patients (p < .0001, r = 0.748). There was no correlation between leptin and DAS-28. The plasma IL-6 and TNF-α did not show significant differences between RA patients and healthy subjects, and also the plasma leptin did not have any correlation with plasma levels of IL-6 and TNF-α.

Conclusion: BMI contribution to RA disease severity is independent of systemic levels of leptin and pro-inflammatory cytokines.

KEYWORDS
Rheumatoid arthritis; leptin; body mass index (BMI); disease activity score-28 (DAS-28); pro-inflammatory cytokines

Introduction

Rheumatoid arthritis (RA) is the most common systemic autoimmune disorder which affects approximately 0.5% to 1% of the adult population with a marked female predilection. RA is characterized by diffuse synovial inflammation that leads to progressive joint damage and disability (Alamanos and Drosos, 2005; Begovich et al., 2004). Although the

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etiology link has not been defined for RA, it has been demonstrated that the interplay between genetic and environmental factors is crucial for the development of RA (Choy and Panayi, 2001). Hormonal effects, alcohol consumption, cigarette smoking, age, gender, socioeconomic status, dietary habits, and obesity are among the major risk factors involved in the development of autoimmune diseases including RA (Di Giuseppe et al., 2014a, 2014b; Jin et al., 2014; Parks et al., 2013). Several lines of evidence have reported an increased risk of RA associated with obesity (Bhole et al., 2011; Fantuzzi, 2005; Stavropoulos-Kalinoglou et al., 2010). Obesity can change the course of the disease and reduce the response to biological treatments (Gremese et al., 2013; Klaasen et al., 2011). Obesity is routinely assessed by the measurement of body mass index (BMI), which is equivalent to the weight in kilograms divided by the square of height in meters (Who, 2004). Some studies have reported a positive relationship between high BMI and increased risk of RA, but others have not confirmed this finding (Bhole et al., 2011; Cerhan et al., 2002; Garcia Rodriguez et al., 2009; Uhlig et al., 1999; Wesley et al., 2013). Adipose tissue actively secretes variable soluble mediators called adipokines (Gronberg, 1994; Ouchi et al., 2011). Leptin is an adipokine (16 kDa) mainly contributes to metabolic reactions, and it also regulates body weight through appetite suppression (Spiegel et al., 2004). Leptin and its receptor (Ob-R) structurally resemble the IL-6 family of cytokines (Palmer and Gabay, 2003), and studies have shown that leptin has a crucial role in the proliferation and differentiation of hematopoietic cells, regulating immune function, stimulation of T-cell-mediated immunity, and inflammatory reactions (Otero et al., 2006; Popa et al., 2005). Leptin augments the production of TNF-α and IL-6 through activation of monocyte/macrophage cells, and it is also involved in inflammatory reaction that occurs in joint disorders like osteoarthritis, psoriatic arthritis, and RA (Faggioni et al., 2001; Versini et al., 2014; Zarkesh-Esfahani et al., 2001) (Figure 1). By their intense inflammatory effects, both TNF-α and IL-6 contribute to the development and maintenance of the ongoing chronic inflammation in RA synovium and the effectiveness of anti-TNF-α and anti-IL-6R monoclonal antibodies in the treatment of RA lend support to this finding (Butler et al., 1995; Chen et al., 2006; Green et al., 1998; Srirangan and Choy, 2010; Yoshizaki et al., 1998). On the other hand, the traditional disease-modifying anti-rheumatic drugs (DMARDs), especially methotrexate (MTX), which is the cornerstone of RA treatment directly or indirectly inhibit the actions of pro-inflammatory cytokine including TNF-α and IL-6 in RA patients (Dénarié et al., 2017; O'dell et al., 1996; Sung et al., 2000; Weinblatt, 1994). For further clarification of existing controversial data, this study aims to address the effect of high BMI and adipokines leptin on plasma levels of pro-inflammatory cytokines and RA disease progression.

Patients and methods

Patients' characteristics

Our study was in accordance with the Declaration of Helsinki and was performed with the approval from the Ethics Committee of Kermanshah University of Medical Sciences (KUMS). All of the people signed informed consent and were informed about the goals and procedures of the research. We have included 50 patients with RA including 20 patients (age, 47.9 ± 2.7 years; 3 men and 17 women) without any treatment and 30 patients (age, 47.9 ± 1.8 years; 6 men and 24

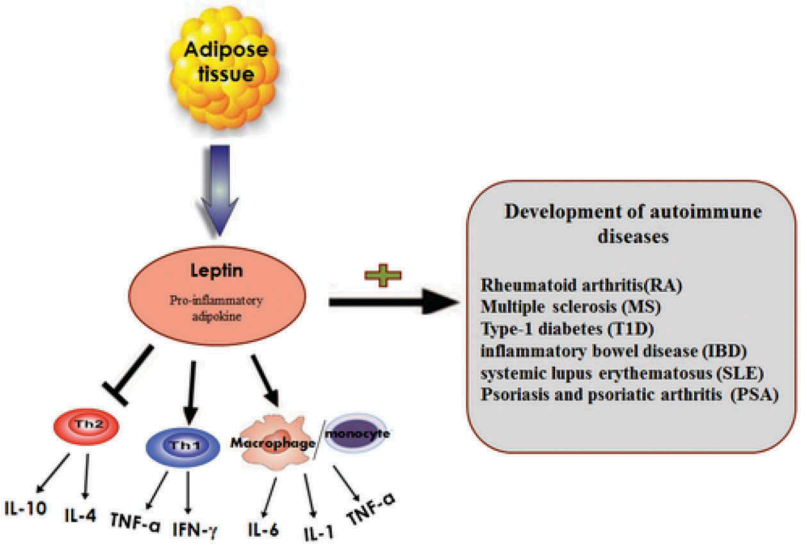

Figure 1. Direct crosstalk between obesity and immune system. Adipose tissue controls different aspects of immune response. Leptin augments the production of TNF-α and IL-6 through activation of monocyte/macrophage cells. Leptin and pro-inflammatory cytokines produced from this tissue play a significant role in the development of various autoimmune diseases.

women) who received MTX (7.5–25 mg/week), HQ (200 mg/day) combinational therapy plus oral PSL (5–10 mg/day). The patients were diagnosed according to the EULAR/ACR 2010 classification criteria by an expert rheumatologist and selected by consecutive sampling between July 2017 and October 2017 from Helal-Ahmar clinic of KUMS. Patients with the history of other rheumatic and autoimmune disease, severe infection, cancer, and pregnant women were excluded from our study. Also, 30 age- and sex-matched healthy subjects (age, 47.6 ± 1.9 years; 6 men and 24 women) were selected as the control group. The demographic information and clinical characteristics of patients and controls are shown in Table 1.

The calculation of body mass index

The measurement of height and weight were done according to standard protocols, with participants wearing light clothing and no footwear. The subject's weight in kilograms was divided by the height in meters squared to calculate BMI. Based on the World Health Organization (WHO) criteria, the BMI was classified into three groups as follows: normal weight (NW) range 18.5–24.9, overweight (OW) 25.0–29.9, and obese (OB) ≥30.0 (kg/m2).

Plasma sample collection

A quantity of 5 ml of peripheral blood was obtained from each patient and healthy people. Plasma samples were separated in Ethylene diamine tetra-acetic Acid (EDTA)-containing tubes and centrifuged at 3000 g for 10 min and were stored at −70°C for later measurement of cytokines.

Table 1. Demographic data and clinical characteristics of RA patients and control group.

Variables		Controls (n = 30)	RA patients Treated (n = 30)	RA patients Untreated (n = 20)
Age	Female	46.12 ± 1.98	46.50 ± 2.07	47.00 ± 3.01
	Male	53.67 ± 4.97	53.50 ± 3.54	53.00 ± 6.42
Min/Max (age)	Female	26/60	26/64	25/67
	Male	40/70	45/67	41/63
Drugs (%)	PRL	0	100	0
	MTX	0	100	0
	HQ	0	100	0
	Other DMARDS	0	0	0
Tests	ESR (mm/h)		15.17 ± 1.79*	29.35 ± 5.34
	Tender joint		1.26 ± 0.23***	6.35 ± 0.83
	Swollen joint		0.73 ± 0.14***	3.00 ± 0.50
	DAS-28		2.43 ± 0.13***	3.91 ± 0.19

Data are Mean ± SEM; PRL dose: 5–10 mg/day, MTX: 7.5–25 mg/week, HQ: 200mg/day *$p < .05$, **$p < .01$, ***$p < .001$. DAS-28: Disease Activity Score-28, DMARD: disease-modifying anti-rheumatic drug, ESR: erythrocyte sedimentation rate, HQ: Hydroxychloroquine, MTX: Methotrexate, PRL: Prednisolone.

The calculation of disease activity score

According to the formula DAS-28 = 0.56 (TJ) ^{½} +0.28 (SJ) $^{1/2}$ + 0.70 ln (ESR) +0.014 GH (TJ: Number of tender joints from 28 joints; SJ: Number of swollen joints from 28 joints; GH: global health), disease activity score was calculated by an expert rheumatologist (Inoue et al., 2007).

Method of cytokine assays

Plasma levels of all cytokines were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (IL-6 Eastbiopharm, Hangzhou, China), (TNF-α IBL, Hamburg, Germany), (Leptin BioVandor, Brno, Czech Republic).

Based on the manufacturer's kit protocol, the minimum concentration of cytokines assays for IL-6, TNF-α, and Leptin were 1.03 ng/L, 2.3 pg/ml, and 0.2 ng/ml, respectively.

Statistical analysis

Data analysis and graph drawing were performed by SPSS software version 24 (SPSS, Chicago, IL, USA), GraphPad Prism version 6 (GraphPad Software, La Jolla, CA, USA), and Microsoft Excel 2010. Data Normality was evaluated using the Kolmogorov-Smirnov (K-S) test. The difference in three main groups, control, under treatment, and newly diagnosed/NW, OW, and OB was calculated with one-way ANOVA with Tukey post-test for parametric data and Kruskal–Wallis test for non-parametric data. The t-test and Mann–Whitney U test were used to compare the parametric and non-parametric data, respectively, between the two groups. Pearson's correlation test was employed to assess the correlations between parametric variables, and also Spearman rank correlations were applied to test the correlation between non-parametric variables. In all statistical analyses, $p < .05$ was considered statistically significant, and the results were expressed as mean ± SEM.

Results

Demographic and clinical variables

Patients and controls were matched regarding to age and gender. ESR values and DAS-28 were significantly higher in patients without treatment compared to undertreatment RA patients ($p = .029$, $p < .001$, respectively) (Table 1).

Seventeen (34%) patients had normal BMI, 23 (46%) were OW, and 10 (20%) were OB (Table 2). There were no differences in variables between patients with NW, OW, and OB. Only OW and OB patients had high plasma leptin levels compared to NW patients (Table 2). Also, experimental and clinical characteristics in separate groups of newly diagnosed and undertreatment patient and healthy subjects were evaluated (Table 3).

BMI and plasma levels of cytokines

The mean BMI (26.39 ± 1.01 kg/m^2, 27.54 ± 0.83 kg/m^2, 25.49 ± 0.84 kg/m^2, $p = .23$) and plasma levels of IL-6 (241.51 ± 39.46 pg/mL, 171.44 ± 13.65 pg/mL, 232.81 ± 31.08 pg/mL, $p = .575$) and TNF-α (7.94 ± 0.44 pg/mL, 8.03 ± 0.41 pg/mL, 7.82 ± 0.35 pg/mL, $p = .921$) did not differ significantly between newly diagnosed RA patients, patients who received a combination of MTX and HCQ plus PSL and control group. The mean plasma levels of leptin in the newly diagnosed RA patients, undertreatment RA patients, and control group were 26.8 ± 2.5 ng/mL, 30.84 ± 2.4 ng/mL, and 18.28 ± 2.3 ng/mL, respectively. Leptin plasma levels in undertreatment patients were significantly higher compared to the healthy subjects ($p = .001$), but there were no significant differences between the newly diagnosed RA patients with both healthy and undertreatment groups ($p = .057$, $p = .516$, respectively) (Figure 2). Leptin levels in total RA patient were higher than healthy subjects ($p = .001$).

Distribution of the body mass index in RA patients and healthy subjects

The t-test analysis did not show any significant difference between the mean BMI in NW and OW RA patients (22.40 ± 0.59, 27.62 ± 0.27, respectively) compared to NW and OW healthy people (21.55 ± 0.75, 26.97 ± 0.39, respectively). The mean BMI in OB patients (34.24 ± 0.69) was significantly higher than the OB healthy subjects (31.46 ± 0.7) (Figure 3).

Table 2. Experimental and clinical characteristics of patients with rheumatoid arthritis who were normal weight (NW), overweight (OW), and obese (OB).

	RA patient			
Variables	RA NW ($n = 17$)	RA OW ($n = 23$)	RA OB ($n = 10$)	p Value
Age	45.11 ± 3.01	47.13 ± 2.13	54.40 ± 2.22	0.089 (a)
ESR (mm/h)	23.70 ± 5.46	17.65 ± 3.36	23.30 ± 4.47	0.347 (b)
Tender joint	3.52 ± 1.05	3.17 ± 0.70	3.2 ± 0.86	0.933 (b)
Swollen joint	1.70 ± 0.45	1.26 ± 0.38	2.4 ± 0.60	0.110 (b)
DAS-28	3.11 ± 0.31	2.86 ± 0.20	3.26 ± 0.25	0.573 (a)
Leptin (ng/mL)	21.06 ± 2.5	31.79 ± 2.5	37.98 ± 2.9	0.001 (a) ***
TNF-α (pg/mL)	8.4 ± 0.58	7.84 ± 0.38	7.65 ± 0.71	0.603 (b)
IL-6 (pg/mL)	239.44 ± 43.9	176.68 ± 20.03	183.91 ± 22.06	0.725 (b)

Data are Mean ± SEM, ESR: erythrocyte sedimentation rate, DAS-28: Disease Activity Score-28, TNF-α: tumor necrosis factor alpha, IL-6: Interleukin-6, ***$p < .001$.
(a): One-way ANOVA with Tukey post-test.
(b): The Kruskal–Wallis Test.

Table 3. Experimental and clinical characteristics in separate groups of newly diagnosed and undertreatment patient and healthy subjects.

	Newly diagnosed RA patient			
Variables	Normal weight (n = 9)	Overweight (n = 7)	Obese (n = 4)	p Value
Age	43.88 ± 4.4	48.28 ± 4.12	56.25 ± 4.51	0.248 (a)
ESR (mm/h)	34.0 ± 9.0	24.14 ± 9.7	28.0 ± 7.4	0.446 (b)
Tender joint	6.11 ± 1.54	6.85 ± 1.37	6.0 ± 0.91	0.820 (b)
Swollen joint	2.77 ± 0.66	2.54 ± 1.08	4.25 ± 0.75	0.245 (b)
DAS-28	3.98 ± 0.35	3.73 ± 0.34	4.09 ± 0.16	0.783 (a)
Leptin (ng/mL)	19.21 ± 3.6	29.88 ± 2.6	38.45 ± 0.9	0.005 (a) **
TNF-α (pg/mL)	7.86 ± 0.64	7.20 ± 0.42	9.41 ± 1.38	0.303 (b)
IL-6 (pg/mL)	278.27 ± 74.91	228.82 ± 59.86	181.0 ± 27.73	0.877 (b)
	Undertreatment RA patient			
Variables	Normal weight (n = 8)	Overweight (n = 16)	Obese (n = 6)	p Value
Age	46.50 ± 4.28	46.62 ± 2.56	53.16 ± 2.44	0.378 (a)
ESR (mm/h)	12.12 ± 2.17	14.81 ± 2.35	20.16 ± 5.71	0.635 (b)
Tender joint	0.62 ± 0.18	1.56 ± 0.39	1.33 ± 0.42	0.249 (b)
Swollen joint	0.50 ± 0.26	0.68 ± 0.19	1.16 ± 0.30	0.248 (b)
DAS-28	2.13 ± 0.24	2.48 ± 0.19	2.70 ± 0.18	0.327 (a)
Leptin (ng/mL)	23.15 ± 3.6	32.68 ± 3.53	37.60 ± 5.5	0.114 (a)
TNF-α (pg/mL)	9.02 ± 1.00	8.13 ± 0.51	6.47 ± 0.24	0.032 (b) *
IL-6 (pg/mL)	195.76 ± 40.46	153.87 ± 10.25	185.85 ± 33.92	0.910 (b)
	Healthy subjects			
Variables	Normal weight (n = 14)	Overweight (n = 9)	Obese (n = 7)	p Value
Age	47.43 ± 3.17	51.44 ± 2.98	43.14 ± 3.21	0.299 (a)
Leptin (ng/mL)	13.30 ± 3.22	22.09 ± 3.82	23.90 ± 5.06	0.116 (a)
TNF-α (pg/mL)	7.81 ± 0.42	7.50 ± 0.46	8.26 ± 1.15	0.794 (b)
IL-6 (pg/mL)	328.57 ± 50.67	125.86 ± 7.11	178.80 ± 52.96	0.017 (b) *

Data are Mean ± SEM, ESR: erythrocyte sedimentation rate, DAS-28: Disease Activity Score-28, TNF-α: tumor necrosis factor alpha, IL-6: Interleukin-6, *$p < .05$, **$p < .01$.
(a): One-way ANOVA with Tukey post-test.
(b): The Kruskal–Wallis Test.

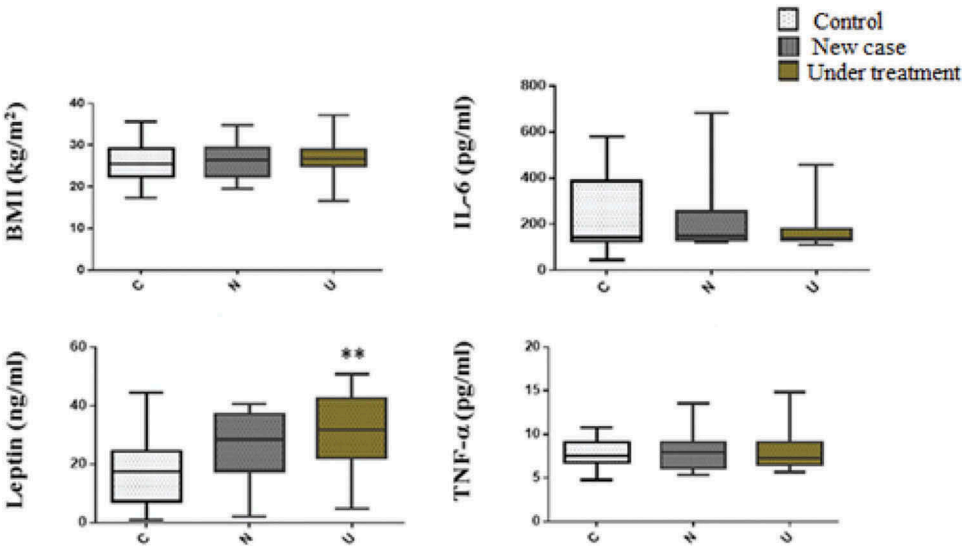

Figure 2. The mean BMI (a) and plasma levels of Leptin (a), TNF-α (b), and IL-6(b) in the newly diagnosed rheumatoid arthritis patients (new case RA), undertreatment patients, and age- and sex-matched control group. (a) One-way ANOVA with Tukey post-test. (b) Kruskal–Wallis test.

**$p < .001$ Leptin plasma levels in undertreatment patients vs Leptin plasma levels in healthy subjects

Correlation between variables

The correlation between BMI with ESR, Tender joint, swollen joint, and DAS-28 in all RA patients (Table 4) and also in separate groups of newly diagnosed and undertreatment patient (Table 5) was investigated. As shown in Figure 4, we could not find any significant correlation between BMI and plasma level of IL-6, in both newly diagnosed and undertreatment patient. There was a positive significant correlation between BMI and plasma level of leptin only in the newly diagnosed patient; besides that, leptin showed a positive correlation with ESR. In addition, we found a negative significant correlation between BMI and plasma level of TNF-α only in undertreatment patient (Figure 4). The correlation between age and BMI, plasma level of leptin with ESR is shown in Figure 5. The study design has been illustrated in Figure 6

Discussion

The contribution of obesity to the RA development, progression, and its associated comorbidities has been explored in the previous studies, but the existing data in this area are not very consistent, (Dar et al., 2018; George and Baker, 2016; Kim et al., 2017). In contrast to the previous studies which showed higher BMI in RA patients, we could not find significant differences in BMI between RA patients and healthy controls and also between newly diagnosed and undertreatment patients (Dar et al., 2018; Del Rincón et al., 2001; Gonzalez et al., 2008). This controversy in various studies may stem from differences in nutritional habits, physical activity, and genetic background. In the following for evaluation of obesity effect on RA progression, we surveyed the association between

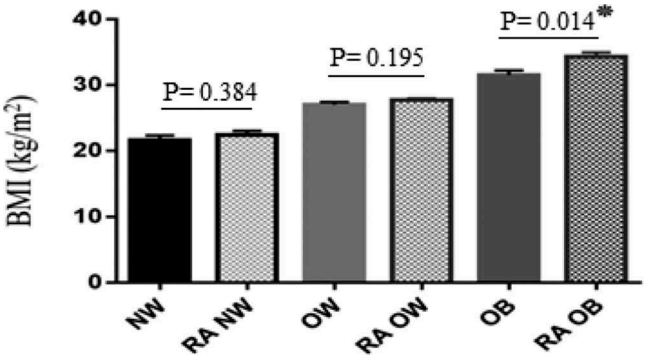

Figure 3. Distribution of the body mass index in RA patients and healthy subjects.

*$p < .05$ RA patients obese vs healthy subjects obeseNW: healthy subjects with normal weightRA NW: RA patients with normal weightOW: healthy subjects with overweightRA OW: RA patients with overweightOB: healthy subjects obeseRA OB: RA patients obese

Table 4. Correlations between body mass index with ESR, number of tender joint, number of swollen joint, and disease activity score in all RA patients.

	RA patient		
BMI	RA NW (n = 17)	RA OW (n = 23)	RA OB (n = 10)
ESR (mm/h) (a)	p = .595 r = 0.139	p = .577 r = 0.123	p = .276 r = −0.382
Tender joint (a)	p = .111 r = −0.401	p = .024 r = 0.468*	p = .156 r = −0.485
Swollen joint (a)	p = .132 r = −0.381	p = .433 r = 0.172	p = .396 r = −0.303
DAS-28 (b)	p = .769 r = −0.077	p = .036 r = 0.440*	p = .088 r = −0.566

BMI: body mass index, DAS-28: Disease Activity Score-28, NW: normal weight range 18.5–24.9, OW: overweight 25.0–29.9, OB: obese ≥30.0 (kg/m2), *$p < .05$.
(a): Spearman's rank correlation.
(b): Pearson's rank correlation.

BMI and DAS-28, a well-established index for both RA severity and its inflammatory activity; we found a significant correlation between DAS-28 and BMI in OW patients in the newly diagnosed and undertreatment patients together, but this correlation was absent when we assessed it in these two groups separately. Other studies also reported a positive association between RA disease activity and obesity (Ajeganova et al., 2013; Crowson et al., 2013; Lu et al., 2014; Symmons et al., 1997). Through the elaboration of pro-inflammatory cytokines, especially TNF-α and IL-6, as well as various adipokines like leptin, adipocytes may contribute to ongoing RA inflammatory process (Deng et al., 2012; Fantuzzi, 2005; Rho et al., 2009; Trayhurn and Wood, 2004). IL-6, TNF-α, and leptin contribute to various aspects of RA pathogenesis, including synovitis, joint damage, and RA-associated comorbidities such as cardiovascular disease (Deng et al., 2012; Feldmann et al., 2001; Hashizume and Mihara, 2011; Panoulas et al., 2009). In our survey, the plasma levels of leptin were significantly higher in RA subjects compared to healthy control which was in

Table 5. Correlations between body mass index (BMI) with ESR, number of tender joint, number of swollen joint, and disease activity score in separate groups of newly diagnosed and undertreatment patient.

	Newly diagnosed RA patient		
BMI	RA NW (n = 9)	RA OW (n = 7)	RA OB (n = 4)
ESR (mm/h) (a)	p = .116 r = 0.561	p = .585 r = −0.252	p = <.001 r = −1***
Tender joint (a)	p = .240 r = −0.437	p = .004 r = 0.917**	p = .60 r = −0.40
Swollen joint (a)	p = .709 r = 0.145	p = .274 r = 0.482	p = .262 r = 0.738
DAS-28 (b)	p = .559 r = 0.226	p = .458 r = 0.339	p = .112 r = −0.888
	Undertreatment RA patient		
BMI	RA NW (n = 8)	RA OW (n = 16)	RA OB (n = 6)
ESR (mm/h) (a)	p = .888 r = 0.060	p = .138 r = 0.387	p = .957 r = −0.029
Tender joint (a)	p = .499 r = −0.282	p = .938 r = 0.021	p = .439 r = −0.395
Swollen joint (a)	p = .067 r = −0.674	p = .864 r = −0.046	p = 1 r = 0.000
DAS-28 (b)	p = .480 r = −0.294	p = .396 r = 0.228	p = .943 r = −0.038

BMI: body mass index, DAS-28: Disease Activity Score-28, NW: normal weight, OW: overweight, OB: obese.
**p < .01, ***p < .001.
(a): Spearman's rank correlation.
(b): Pearson's rank correlation.

parallel with the previous studies (de Resende Guimarães et al., 2018a; Gunaydin et al., 2006; Ismail et al., 2011). In contrast, Nishiya K and his colleagues could not find a significant difference in serum leptin between RA patients and control (Nishiya et al., 2002). Similar to the previous studies, we also observed a significant correlation between plasma levels of leptin and BMI, but just in our newly diagnosed patients (de Resende Guimarães et al., 2018b; Nishiya et al., 2002). Lack of association between BMI and leptin in undertreatment patients may stem from the DMARD regimen effects on leptin production (Bokarewa et al., 2003). For further clarification of leptin role in RA disease activity, we evaluated the association between plasma leptin and DAS-28, but we did not find a significant correlation between these two variables which was in concordance with the study of Abdalla M et al. (*Ab*dalla et al., 2014). In contrast to our finding, B Targońska-St ępniak and his colleagues reported a positive correlation between plasma leptin and DAS-28 (Targońska-Stępniak et al., 2008). The reason for these very conflicting results may be related to the various factors such as the type of therapeutic regimen, the stage of disease, and the heterogeneous feature of RA disease entity itself with regard to underlying pathological mechanisms. Although leptin promotes inflammatory reactions through the induction of TNF-α and IL-6 biosynthesis, similar to Gunaydin R et al., we could not find any correlation between plasma levels of leptin and plasma concentration of pro-inflammatory cytokines (Gunaydin et al., 2006). Besides that, we found no differences in plasma concentration of TNF-α and IL-6 between healthy subjects and RA patients. Our result showed that the contribution of leptin in the pro-inflammatory reactions which is

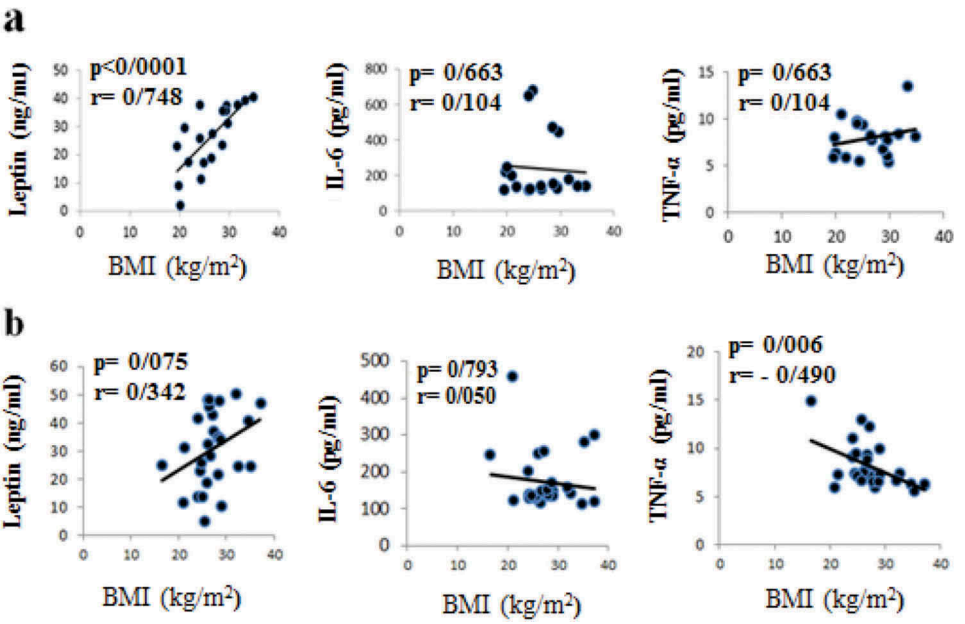

Figure 4. Correlations between study variables.

Correlations between BMI with Leptin, IL-6, and TNF-α in both newly diagnosed and undertreatment RA patients.a = newly diagnosed patientb = undertreatment patientThere was a positive significant correlation between BMI and plasma level of leptin in newly diagnosed patients and a negative significant correlation between BMI and plasma level of TNF-α in undertreatment patients

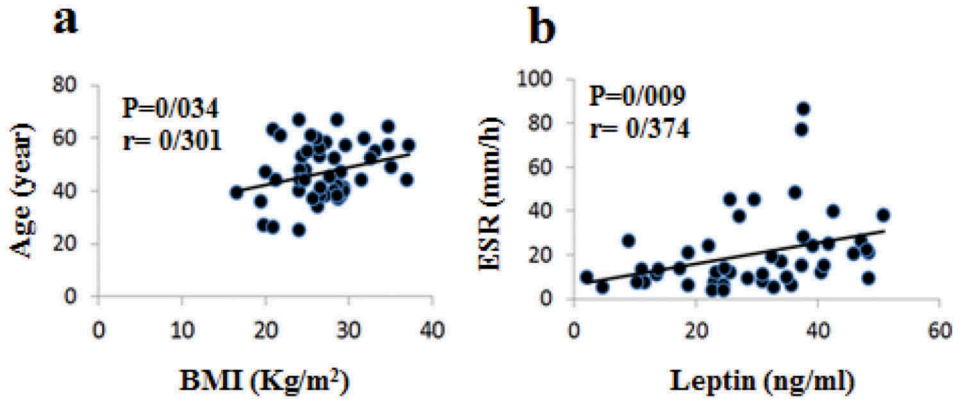

Figure 5. Correlations between study variables.

(a): Correlations between BMI and Age (*p < .05 positive significant correlations)Pearson's rank correlation(b): Correlations between Leptin and ESR (**p < .01, positive significant correlation) Spearman's rank correlation

showed in the previous study in RA patients is independent of plasma levels of pro-inflammatory cytokines like TNF-α and IL-6.

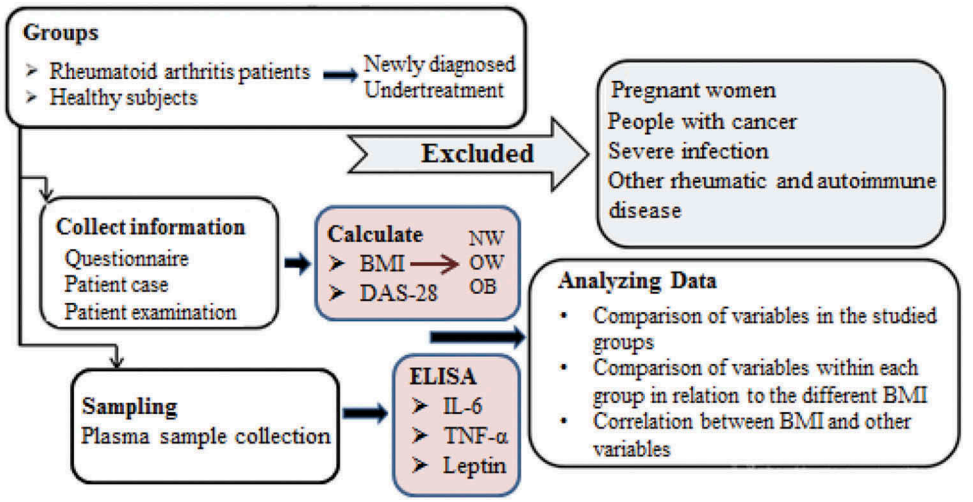

Figure 6. Protocol design of this study.

DAS-28: Disease Activity Score-28, BMI: body mass index, NW: normal weight, OW: overweight, OB: obese, TNF-α: tumor necrosis factor alpha, IL-6: Interleukin-6.

Conclusion

It can be concluded that contribution of high BMI to the clinical progression of RA is independent of the plasma levels of leptin and pro-inflammatory cytokines, and further studies are warranted to find the mechanisms of obesity contribution to RA disease severity.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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