TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2009; 39 (3): 447-451
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-0801-13

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Received: January 25, 2008
Accepted: December 03, 2008

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Plasma resistin and leptin levels in overweight and lean patients with rheumatoid arthritis

Aim: Adipocytokines are now considered important players in the etiopathogenesis of numerous metabolic and inflammatory disorders. However, plasma leptin and resistin levels in rheumatoid arthritis (RA) are still unclear. We aimed to investigate the plasma levels of leptin and resistin in patients with rheumatoid arthritis and to compare them with controls.

Materials and Methods: Consecutive 52 patients with RA were compared with 52 control subjects in terms of mean leptin and resistin levels.

Results: Patients with RA showed considerably higher plasma levels of leptin (34.3 ± 27.9 vs. 11.1 ± 4.1) and resistin (4.8 ± 0.7 vs. 4.0 ± 1.3) than healthy controls ($P < 0.0001$). There was no significant difference regarding age, duration of disease, sex, CRP, and leptin and resistin levels between overweight and lean RA subjects. Plasma leptin level was significantly correlated with ESR (Erythrocyte Sedimentation Rate) ($r = 0.287$, $P = 0.039$) and swollen and tender joint count ($r = 0.563$, $P < 0.0001$) but not with resistin in subjects with RA. Measuring the plasma leptin level may be a potential marker of disease activity in RA.

Conclusions: Studies including more RA patients might be needed to define the role of leptin and resistin in RA subjects.

Key Words: Rheumatoid arthritis, Leptin, Resistin, Body mass index, Disease activity

Zayıf ve aşırı kilolu hastalardaki plazma leptin ve rezistin düzeyleri

Amaç: Çok sayıdaki metabolik ve inflamatuar bozukluğun etiopatogenezinde adipositokinlerin önemli bir rol oynadığı düşünülmektedir. Fakat, romatoid artiritli hastalardaki plazma leptin ve rezistin düzeyleri henüz belirsizdir. Biz bu araştırmada romatoid artiritli hastalardaki plazma leptin ve rezistin düzeylerini araştırmayı ve bunları kontroller ile karşılaştırmayı amaçladık.

Yöntem ve Gereç: Romatoid artiritli 52 hastanın leptin ve rezistin düzeyleri 52 kontrol örneği ile karşılaştırıldı.

Bulgular: Romatoid hastalardaki plazma leptin (34,3 ± 27,9'a karşın 11,1 ± 4,1) ve rezistin (4,8 ± 0.7'ye karşın 4.0±1.3) düzeyleri sağlıklı kontrollere göre oldukça yüksek olduğu gösterildi ($P < 0.0001$). Zayıf ve aşırı kilolu Romatoid Artiritli vakaların yaş, hastalık süreci, cinsiyet, CRP, ve leptin ve rezistin düzeyleri arasında önemli bir farklılık bulunamadı. Plazma leptin düzeyinin ESR (Eritrosit Sedimentasyon Hızı) ($r = 0.287$, $P = 0.039$) ve şiş ve ağrılı eklem sayısı ($r = 0.563$, $P < 0.0001$) arasındaki korelasyon istatistiksel olarak anlamlı olmasına rağmen, rezisitinde bu korelasyon bulunamadı. Plazma leptin düzeyinin ölçümü, romatoid artirit hastalığının aktivitesini göstermede potansiyel bir marker olabilir.

Sonuç: Romatoid artiritli vakalarda leptin rezistinin oynadığı rolü açıklamak için, daha fazla sayıda romatoid artiritli hastanın dahil olduğu çalışmaların yapılmasına ihtiyaç vardır.

Anahtar Sözcükler: Romatoid Artirit, Leptin, Rezisitin, Vücut Kitle İndeksi, Hastalık Aktivitesi

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition characterized by polyarthritis and severe change in body mass and neuroendocrine environment.

Adipocytokines are now considered as important players in the etiopathogenesis of numerous metabolic and inflammatory disorders including rheumatoid arthritis (1).

Leptin is mainly produced in white adipose tissue and regulates the balance between food intake and energy expenditure. Its plasma levels are correlated with the total body fat mass (2). Leptin levels were found to increase acutely with infectious stimulation and inflammation (3); however, the effect of chronic inflammatory diseases, such as rheumatoid arthritis (RA), on plasma leptin levels is still unknown (4). Plasma leptin levels were correlated with the presence of RA, and disease activity in some reports (4,5). However, in another group of studies, it was neither increased in RA nor correlated with and disease activity (6,7).

Resistin is a newly discovered protein primarily produced mainly by mononuclear cells. It was initially considered as a potential link between obesity and insulin resistance (8). However, interaction with insulin resistance is not clear at all. It belongs to the family of resistin-like molecules. In human subjects resistin appears to act as a critical mediator of the insulin resistance associated with sepsis and possibly with other inflammatory conditions (9,10). Although the plasma resistin level was correlated with presence of RA and disease activity in some reports (11,12), in another group of studies it was not increased in RA when compared with control subjects or correlated with disease activity markers (13, 6).

Therefore, we aimed to compare the plasma levels of adipocytokines associated with inflammation and obesity (leptin, resistin) in patients with rheumatoid arthritis and healthy controls. We also compared lean and overweight subjects with RA regarding leptin and resistin.

Materials and Methods

Consecutive 52 patients who fulfilled the American College of Rheumatology classification criteria for RA (14) were diagnosed with RA at Dicle University School of Medicine, and were enrolled in this study. Patients with history of diabetes mellitus, infection, any systemic illness other than RA, those who had been treated with corticosteroids (>8 mg/day) within 3 months prior to this study, or with unstable weight history were excluded from the study. Treatments at the time of sampling were as followed: methotrexate in 50 patients, sulfasalazine in 7 patients, and methyl prednisolone in 11 patients (2-6 mg/day). Demographic data of the subjects are given in Table 1. The control group consisted of 52 gender-, BMI-, and age-matched hospital staff members. Informed consent was obtained from patients and controls according to the declaration of Helsinki; the design of the work was approved by the Ethical Committee of the hospital.

In all participants, blood was collected into Vacutainer tubes containing EDTA between 9.00 AM and 11.00 AM after overnight fasting. For the determination of leptin plasma levels, a commercial high-sensitive ELISA kit was used (BIOSOURCE, 542 Flynn Road, Camarillo, CA 93012). Sensitivity was 0.018 ng/ml. Plasma resistin levels were determined by a specific ELISA assay using materials and protocols supplied by the provider (IMMUNDIAGNOSTIK AG, Stubenwald-Allee 8a, D 64625 Bensheim). Sensitivity was 0.068 ng/ml. We used nephelometric assays for CRP (BECKMAN/COULTER, USA, 2004). ESR was measured with a Greiner analyzer (SET-RATE SCREENER).

Body weights were measured without shoes and in light clothing. Body heights were measured without shoes and/or cap, and were recorded to the nearest centimeter. Body mass index (BMI) was expressed as weight (kilograms) divided by height (meters) squared. The term overweight was defined as individuals having BMI = or > 25 kg/m^2.

Results were expressed as mean ± standard deviations. Comparison of adipocytokine levels between RA patients and controls as well as between the overweight and lean RA patients was repeated using Mann-Whitney U test and chi-square for

frequencies. We used Fisher's exact test values for frequencies lower than 5. A P value less than 0.05 was considered statistically significant and 95% confidence intervals for the differences between proportions were calculated. Spearman's correlations were used. All patients gave informed consent to participate in this study.

Results

No marked difference was observed in BMI, age, and sex between patients and controls (Table 1). Patients with RA showed considerably higher plasma levels of leptin and resistin than healthy controls (Figure 1). As would be expected, CRP and ESR were higher in RA patients than in control subjects.

We also compared the RA subgroups based on BMI. The first one was the lean RA group (mean BMI 23.1 ± 1.5, n = 27) and the second one was the overweight RA group (mean BMI 28.6 ± 1.8, n = 25). There were no significant differences regarding age, duration of disease, sex, the number of swollen and tender joints, CRP, and leptin and resistin levels. ESR was significantly higher in the lean RA subjects compared to the overweight RA subjects.

We analyzed the correlation coefficients between disease activity markers and leptin and resistin levels. ESR has a borderline correlation with leptin (r = 0.287, P = 0.039), significantly correlated with the number of swollen and tender joints (r = 0.563, P < 0.0001), but not with resistin in the subjects with RA. Leptin was significantly correlated with the number of swollen and tender joints (r = 0.395, P = 0.004). In addition, leptin was significantly correlated with ESR (r = 0.432, P = 0.024) and BMI (r = 0.477, P = 0.012) in the control subjects. There was no significant correlation between resistin and age, BMI, ESR, and CRP.

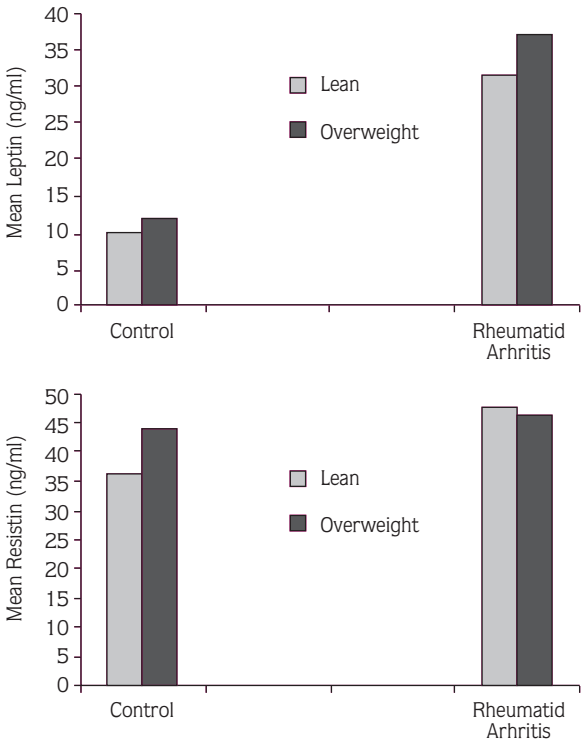

Figure 1. Bars comparing plasma levels of leptin and resistin in lean and overweight RA and lean and overweight controls.

Table 1. Comparison of subjects with RA and control.

	RA n = 52	Control n = 52	P
BMI (kg/m^2)	25.8 ± 3.3	25. 7 ± 3.7	ns*
Age (years)	46 ± 12	47 ± 12	ns
Sex (F/M)	40/12	40/12	ns
CRP (mg/L)	54.0 ± 46.3	7.2 ± 3.2	P < 0.0001
ESR (mm/h)	54.6 ± 22.3	7.6 ± 3.7	P < 0.0001
Leptin (ng/ml)	34.3 ± 27.9	11.1 ± 4.1	P < 0.0001
Resistin (ng/ml)	4.8 ± 0.7	4.0 ± 1.3	P < 0.0001

*: statistically non-significant

Table 2. Comparison of overweight and lean RA.

	RA n = 27	Control n = 25	P
BMI (kg/m2)	23.1 ± 1.5	28.6 ± 1.8,	P < 0.0001
Age (years)	45.4 ± 13.4	48.0 ± 10.5	ns*
RA duration (years)	10.8 ± 8.2	10.4 ± 7.0	ns
Sex (F/M)	21/6	19/6	ns
CRP (mg/l)	53.0 ± 50.9	55.1 ± 41.6	ns
ESR (mm/h)	60 ± 20	48 ± 22	P = 0.066
Leptin (ng/ml)	31.6 ± 28.8	37.2 ± 27.2	P = 0.41
Resistin (ng/ml)	4.9 ± 0.9	4.8 ± 0.3	P = 0.61

*: statistically non-significant

Discussion

In this study, we found a significant increase in plasma leptin and resistin levels in the RA patients compared to the healthy control subjects. We also found that, leptin levels were correlated significantly with ESR levels, which is a known marker for the activity of RA. However, resistin is not correlated with any markers of RA activity.

A marked increase in plasma levels of leptin, adiponectin, and visfatin was noted in patients with rheumatoid arthritis, whereas resistin levels were similar to those observed in healthy controls. They suggested that resistin level is probably not one of the main signals associated with the pathogenesis of this disease (6). On the other hand, other studies with a similar design reported that plasma resistin levels were significantly increased in RA patients and correlated with inflammatory markers and TNF-alpha, suggesting that resistin may play a role in the rheumatoid inflammatory process (11,12). It was also speculated that resistin accumulates locally in the inflamed joints of patients with rheumatoid arthritis (RA) and that its levels correlate with the intensity of inflammation as defined by the intra-articular white blood cell count and IL-6 levels (13). Furthermore, the resistin levels in RA synovial fluid showed a significant correlation with the synovial leukocyte count ($r = 0.66$, $P = 0.003$) and IL-6 levels ($r = 0.36$, $P = 0.014$). In contrast, resistin levels in blood were not related to the duration of RA, age of the patients, circulating C-reactive protein levels, or white blood cell counts (13). We found that resistin levels were significantly higher than the control subjects and were similar in the overweight and lean RA subjects, and no correlation was present between resistin levels and inflammatory markers of RA. Resistin is a potent proinflammatory adipokine that may be involved in the pathogenesis of RA. However, plasma levels are not well correlated with known markers of RA, and synovial values may be more useful as previously reported (13).

In Nishiya et al.'s (5) study including 49 RA patients and 20 healthy individuals; there were no significant differences at plasma leptin levels between patients with RA and the control group. Although it was noticed in their study that plasma leptin levels were correlated with BMI but it was not correlated with ESR and CRP levels. In another study with similar results, 58 RA patients were evaluated and it was shown that plasma leptin levels were correlated with the percent body fat but not correlated with disease activity (4). A few previous reports showed increased plasma leptin levels in patients with RA compared to healthy controls (6,7). Also significant elevations in plasma leptin levels were found in RA patients with high disease activity (15). In our study we detected a significant increase in plasma leptin levels in the RA patients compared to the healthy control subjects. Thus, it is possible that leptin might have an important role in the pathogenesis of RA as a proinflammatory cytokine. Leptin was correlated with ESR but not with BMI in our study. This result is compatible with the literature. However, the role of leptin as a marker of disease activity in RA is still unclear. Plasma leptin in our control subjects was correlated with BMI. However, this correlation was not observed in the subjects with RA, which means that impact of BMI on leptin levels may be blunted by presence of RA.

These different results of clinical studies evaluating leptin and resistin levels in RA patients suggest us further studies in RA patients with methodological additions including related parameters are needed to clarify the effects of leptin in RA. Our study was limited by a small number of subjects and absence of synovial fluid analysis. In the future, other studies including more RA patients might be needed to precise the role of leptin and resistin in RA subjects. Besides, measuring other previously described serological markers reflecting the disease activity of RA, measuring the plasma leptin level, may be a potential marker of disease activity in patients with RA.

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