Serum leptin level in the patients with rheumatoid arthritis : an useful marker for monitoring disease activity

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ABSTRACT

Serum leptin level in the patients with rheumatoid arthritis : an useful marker for monitoring disease activity

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Objectives: To investigate whether serum leptin levels are elevated in patients with active rheumatoid arthritis (RA) and they correlate with disease activity in patients with RA.

Methods: Fifty patients with RA were enrolled and their disease activities were assessed using the Disease Activity Score 28 (DAS28). All patients were divided into two groups according to DAS28: active group enrolled 26 patients and inactive group enrolled 24 patients. Body mass index (BMI) and Homeostasis Model Assessment (HOMA) index for insulin resistance were calculated and serum leptin levels were determined using antibody primate radioimmunoassay. Lipid profiles, including triglyceride and high-density lipoprotein-cholesterol levels also were measured.

Results: Patients with active RA had significantly higher mean serum leptin level compared to those with inactive disease (14.20 ± 10.92 ng/ml versus 7.00 ± 3.42 ng/ml, p=0.003). Mean leptin levels adjusted to BMI were 0.64 ± 0.47 ng m2/ml kg for active RA group and 0.34 ± 0.17 ng m2/ml kg for inactive RA group, and these levels also exhibited a significant difference between groups (p=0.004). Serum

leptin levels and leptin levels adjusted to BMI correlated well with both DAS28 (r=0.363, *p*=0.009 and r=0.368, *p*=0.009) and CRP levels (r=0.433, *p*=0.002 and r=0.472, *p*=0.001) respectively.

Conclusions: Serum leptin levels were significantly elevated in patients with active RA, and correlated well with disease activity. These findings suggest that serum leptin levels might be an useful marker for monitoring disease activity in patients with RA.

Key words: rheumatoid arthritis, disease activity, leptin, body mass index

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I. INTRODUCTION

Leptin is a 16-kDa non-glycosylated protein encoded by the obese (ob) gene, which is located on human chromosome 7. Leptin is mainly produced in white adipose tissue and regulates the balance between food intake and energy expenditure. After leptin is released into the circulation, its plasma levels correlated with total body fat mass.[1, 2] Moreover, previous studies have provided compelling evidence that leptin has actions in the immune system. Leptin has a structural similarity to type I cytokine family and its receptor is a member of the class I cytokine receptor family. Centrally, leptin affects thymic function, leading to the generation and proliferation of naïve T lymphocytes. In the periphery, leptin augments the differentiation of T lymphocytes to T helper-1 lymphocytes, which predominantly secret pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and interferon (IFN)-γ.[3-6]

Rheumatoid arthritis (RA) has a characteristic feature of polyarticular synovitis and bony erosions, and the role of these pro-inflammatory cytokines has been implicated in the development and progression of the disease.[7,8] Thus, there is a possibility that leptin, as a pro-inflammatory cytokine, might have an important role in the pathogenesis of RA, and previous studies evaluated the role of leptin in RA.[9-11] However, there is still a controversy regarding the role of leptin in pathogenesis of

RA, and this might be because of the presences of the confounding factors, including sex, menopausal status, body mass index (BMI), and insulin resistance, which can significantly alter leptin levels.

To avoid these potential biases, we evaluated serum leptin levels in pre-menopausal female patients with RA, and investigated its correlation with disease activity of RA, after adjusting its levels to BMI.

II. MATERIALS AND METHODS

This cross sectional study included 50 pre-menopausal female patients (mean age 40.7 ± 10.2 years, range 16-54 years). All patients were seen at Division of Rheumatology, Severance Hospital, Yonsei University Medical Center, Seoul, Korea between August 2004 and January 2005, and fulfilled the American College of Rheumatology classification criteria for RA.[12] A mean disease duration was 15.5 ± 9.6 months (range 2-35 months). To remove the confounding factors influencing serum leptin levels, we excluded the patients with obesity, which was defined as having BMI > 25 kg/m², diabetes mellitus or fasting glucose > 100 mg/dl, hypertension, and systemic illness other than RA and those who had been treated with corticosteroids (>5mg/day) prior to study enrollment. Body mass index (BMI) was calculated as weight/height² (kg/m²) and disease activities of each patient were assessed using the Disease Activity Score 28 (DAS28).[13] All patients were divided into two subgroups according to their disease activity: active disease group with DAS28 > 3.2 (n = 26) and inactive disease group with DAS28 ≤ 3.2 (n = 24).

The serum leptin levels were measured using radio-immunoassay (RIA, Linco Research, Inc., St. Charles, MO, USA) according to the manufacturer's protocol. Serum levels of fasting glucose, fasting insulin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), triglyceride (TG), and high density lipoprotein (HDL)-cholesterol were also measured. The Homeostasis Model Assessment (HOMA) index was calculated to determine insulin resistance.

All data were shown as mean ± SD. The comparison of clinical and laboratory variables between active and inactive disease groups were performed using Mann-Whitney U test, and the correlations were evaluated using Pearson's correlation test. P values less than 0.05 were considered statistically significant.

III. RESULTS

The clinical and laboratory characteristics of patients with RA were summarized in table 1. The mean age, mean disease duration, the uses of medications and BMI were not different between active and inactive disease groups. HOMA index for insulin resistance and TG over HDL-cholesterol ratio were not different between groups, either. However, mean ESR (p = 0.005) and mean CRP level (*p*=0.01) were significantly higher in patients with active disease than in those with inactive disease (Table1).

Table 1. The characteristics and laboratory findings in the patients with rheumatoid arthritis according to disease activity

	Active RA patients (n=26)	**Inactive RA patients (n=24)**	***P* value**
Age (years old)	42.34 ± 10.31	38.88 ± 9.93	NS
Disease duration	14.89 ± 8.91	16.13 ± 10.42	NS
BMI (kg/m2)	21.48 ± 2.89	20.75 ± 2.78	NS
Glucose (mM/L)	4.79 ± 0.47	4.69 ± 0.39	NS
Insulin (mU/L)	6.71 ± 5.56	6.03 ± 6.60	NS
HOMA-IR	1.42 ± 1.13	1.29 ± 1.53	NS
TG/HDL-cholesterol	2.23 ± 1.79	1.57 ± 0.62	NS
ESR (mm/hr)	**45.96 ± 34.62**	**19.38 ± 14.29**	**0.005**
CRP (mg/dl)	**1.43 ± 1.99**	**0.39 ± 0.81**	**0.010**

NS = no significance

BMI = body mass index, HOMA-IR = Homeostasis Model Assessment index for insulin resistance,

TG = triglyceride,

HDL = high density lipoprotein, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein

Patients with active disease had significantly higher mean leptin level than those with inactive disease (p = 0.003), and mean leptin level adjusted to BMI (leptin/BMI) of patients with active disease also showed a significant elevation compared to that of those with stable disease (p = 0.004) (Figure 1). Leptin levels and leptin levels adjusted to BMI exhibited significant correlations with both DAS28 (r = 0.363, p = 0.009 and r=0.368, p=0.009) and CRP levels (r = 0.433, p = 0.002 and r=0.472, p=0.001) (Figure 2)

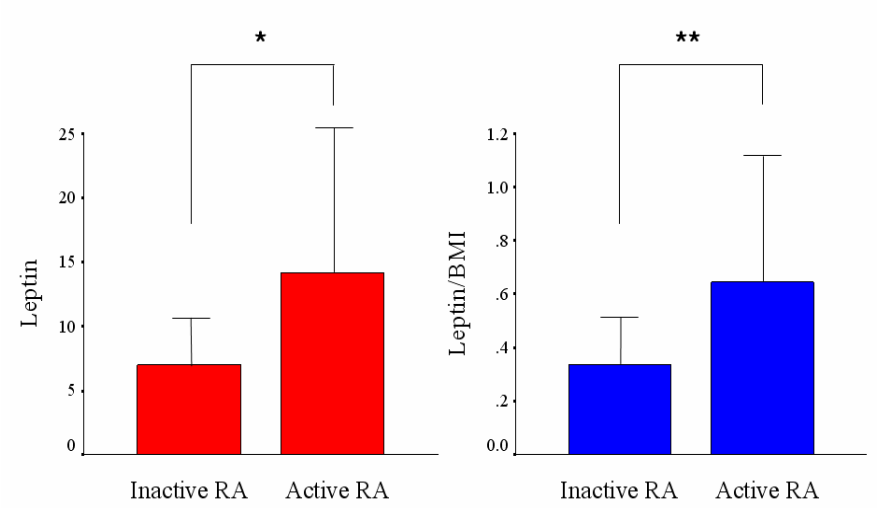

Figure 1. Serum level of leptin and leptin adjusted to BMI according to disease activity

Patients with active RA had significantly higher mean serum leptin level compared to those with inactive disease (14.20 ± 10.92 ng/ml versus 7.00 ± 3.42 ng/ml, p=0.003). Mean leptin levels adjusted to BMI were 0.64 ± 0.47 ng m2/ml kg for active RA group and 0.34 ± 0.17 ng m2/ml kg for inactive RA group, and these levels also exhibited a significant difference between groups (p=0.004).

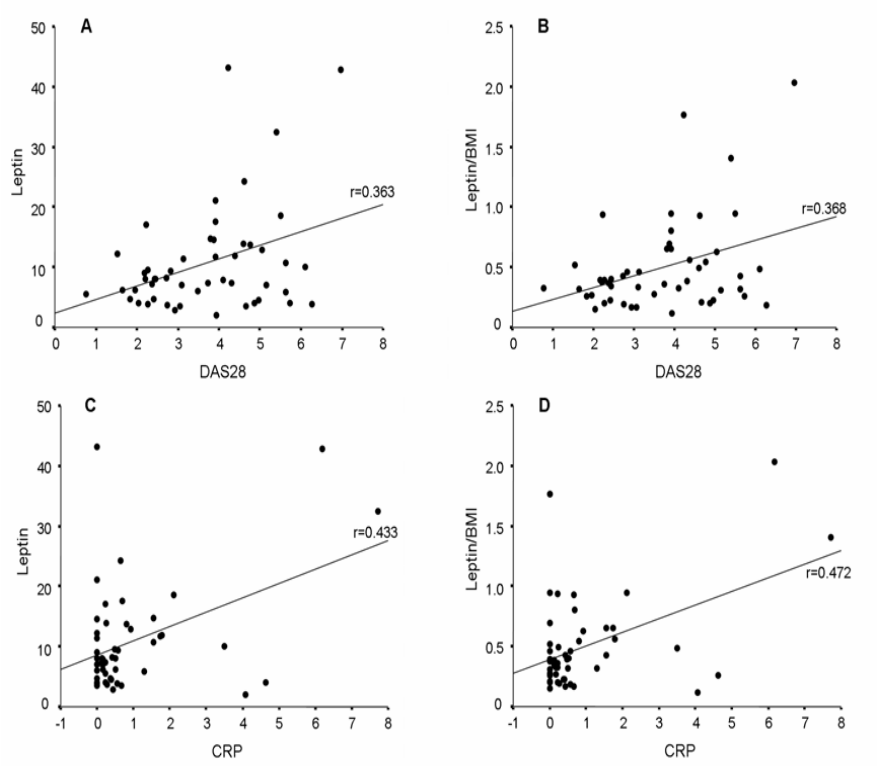

Figure 2. Correlation of leptin with markers for disease activity.

IV. DISCUSSION

In this study, we found a significant increase of serum leptin levels in patients with active RA compared with those with inactive disease. Moreover, increased leptin levels correlated well with clinical and laboratory parameters, reflecting disease activity of RA. These data supports the previous findings by Bokarewa et al.[10] They documented that leptin production was significantly increased in patients with RA compared with healthy controls. Besides its primary role of regulating energy expenditure, it has been recognized that leptin induces the activation of monocytes and T lymphocytes and enhances their release of pro-inflammatory cytokines, such as TNF-α, IL-6, and IFN-γ.[3-5] Also, leptin itself can be up-regulated by many acute phase factors, including inflammatory cytokines.[6] Thus, the significant associations of leptin levels with DAS28 and CRP levels observed in this study support the possible role of leptin in the pathogenesis of RA. However, recent study on the levels of leptin in patients with RA showed inconsistent results. Anders et al found that plasma leptin concentrations did not differ between RA patients and controls and Popa et al showed that baseline concentrations of leptin were inversely correlated with the degree of inflammation as assessed by CRP and IL-6 concentrations.[9,11]

It is well established that dyslipidemia is commonly encountered in patients with RA[14] and a recent study revealed a strong association between inflammatory activity and insulin resistance in patients with RA.[15] Since leptin is regulated by various factors, including sex hormones, insulin resistance, dyslipidemia, and body fat mass, it is difficult to clearly define the role of leptin and these potential biases may cause the inconsistency on the leptin levels in patients with RA. Unlike with the study by Bokarewa et al, we enrolled only pre-menopausal women who do not have obesity and impaired glucose metabolism to exclude these potential biases. Thus, the only contributor to the increase of leptin levels observed in this study is the disease activity of RA, and its strong association with disease activity suggests that the measurement of leptin levels might be used for monitoring disease activity of RA.

Unfortunately, this study has a limitation: since this study was designed as a cross-sectional study at the entry, it was relevant to figure out the association between leptin level and disease activity, but it was not sufficient to clarify the change of leptin levels in the patients with RA according to the time course of disease. Thus, further study is needed to overcome this limitation.

V. CONCLUSION

In summary, we found strong correlations of serum leptin with or without adjustment with BMI with disease activity of RA. This finding indicates the usefulness of measurement of leptin levels for monitoring disease activity in patients with RA and suggests the possible pathogenic role of leptin in the disease.

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ABSTRACT

류마티스관절염 환자의 혈청 렙틴 :질병 활성도의 예측인자

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목적 : 류마티스관절염 환자에서, 혈청 렙틴(leptin)의 류마티스 관절염의 활성도와의 연관성을 조사함으로써, 질병 활성도의 예측인자로서의 역할을 고찰하였다.

방법 : 50명의 류마티스관절염 환자가 본 연구에 참여하였고, Disease Activity Score 28 (DAS28)를 이용, 질병의 활성도를 측정하여 DAS28가 3.2를 초과하는 환자군을 활성군으로 규정하였고, 3.2 이하인 환자군을 비활성군으로 규정하였다 (활성군 26명, 비활성군 24명). 체질량지수(Body Mass Index, BMI)와 인슐린저항성의 지표인 Homeostasis Model Assessment index (HOMA-IR)를 계산하였고, 혈청 렙틴, 중성지방, 고밀도 콜레스테롤, ESR, CRP 등을 측정하였다.

결과 : 활성군의 혈청 렙틴이 비활성군보다 높게 측정되었고 (14.20 ± 10.92 ng/ml vs 7.00 ± 3.42 ng/ml, p=0.003), 체질량지수에 대해 보정한 혈청 렙틴도 활성군에서 유의하게 높았다 (0.64 ± 0.47 ng m2/ml kg vs 0.34 ± 0.17 ng m2/ml kg, p=0.004). 또한, 혈청 렙틴과 체질량지수에 대해 보정한 혈청 렙틴은 각각, 질병의 활성도를 잘 반영하는 DAS28 (r=0.363, p=0.009 and r=0.368, p=0.009)과 CRP (r=0.433, p=0.002 and r=0.472, p=0.001) 와 정비례관계를 보였다.

결론 : 류마티스관절염 환자의 혈청 렙틴은 활성군에서 유의하게 높게 측정되었고, 질병의 활성도와 비례하였다. 따라서 혈청 렙틴은 류마티스관절염 환자의 질병의 활성도를 반영하는 유용한 지표로서

의미가 있다.

핵심되는 말 : 류마티스관절염, 질병활성도, 렙틴, 체질량지수