

# Elevated Serum Levels of Resistin, Leptin, and Adiponectin are Associated with C-reactive Protein and also Other Clinical Conditions in Rheumatoid Arthritis

Takumi Yoshino<sup>1</sup>, Natsuko Kusunoki<sup>1</sup>, Nahoko Tanaka<sup>1</sup>, Kaichi Kaneko<sup>1</sup>, Yoshie Kusunoki<sup>1</sup>, Hirahito Endo<sup>1</sup>, Tomoko Hasunuma<sup>1,2</sup> and Shinichi Kawai<sup>1</sup>

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## Abstract

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**Objective** Body fat is an important source of hormones and cytokines (adipokines) that not only regulate the energy balance, but also regulate the inflammatory and immune responses. This study investigated the association of clinical conditions with serum levels of adipokines in patients with rheumatoid arthritis.

**Methods** Serum levels of resistin, leptin, and adiponectin were measured by enzyme-linked immunosorbent assay in 141 patients (110 women) who fulfilled the 1987 revised criteria of the American Rheumatism Association for the diagnosis of rheumatoid arthritis and in 146 normal controls (124 women). Then the correlations between adipokine levels and clinical parameters were evaluated.

**Results** The serum resistin level did not differ between the patients and controls. However, serum leptin levels were significantly higher in male and female rheumatoid arthritis patients than in the corresponding controls, while the serum adiponectin level was significantly higher in female patients than in female controls. Multivariate analysis revealed that predictors of an elevated resistin level were female sex and C-reactive protein (CRP), while the leptin level was related to the body mass index and CRP. Predictors of an elevated adiponectin level were the use of prednisolone and CRP, however, CRP was negatively associated with adiponectin in patients with rheumatoid arthritis.

**Conclusion** The serum levels of resistin and leptin were positively associated with CRP level in patients with rheumatoid arthritis, suggesting that these adipokines may act as pro-inflammatory cytokines in this disease. The serum adiponectin level was elevated in the patients, however, it was negatively associated with CRP level. In addition, the serum levels of resistin, leptin, and adiponectin were also associated with female sex, BMI and the use of prednisolone, respectively.

**Key words:** rheumatoid arthritis, resistin, leptin, adiponectin, C-reactive protein

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## Introduction

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that is characterized by symmetrical synovitis, progressive joint damage, pain, fatigue, and disability. Although the exact cause of this disease is still unknown, investigation of its pathogenesis has confirmed a role for various pro-inflammatory cytokines, including tumor

necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin-1 (IL-1), and interleukin-6 (IL-6) (1-3). Accordingly, inhibition of these cytokines has become the new therapeutic strategy for RA.

Recent studies have demonstrated that cytokines secreted by adipocytes (adipokines) have an important physiological role. Adipokines, including resistin, leptin, and adiponectin, have been demonstrated to influence eating behavior and the energy balance, and have also been noted as new mediators of the inflammatory process (4, 5). Recently, we reported

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<sup>1</sup>Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine, Japan and <sup>2</sup>Research Center for Clinical Pharmacology, Kitasato University, Japan

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Correspondence to Dr. Shinichi Kawai, skawai@med.toho-u.ac.jp

**Table 1. Demographic Profile of the Patients with Rheumatoid Arthritis and Control Subjects**

	Sex	RA patients (n=141)	Control subjects (n=146)	p value
Male : Female		31:110	22:124	
Age (years)	M	61.0 ± 12.7	45.6 ± 13.8	<0.001
	F	59.0 ± 14.0	57.5 ± 16.6	0.456
Height (cm)	M	166.8 ± 6.1	170.0 ± 6.2	0.069
	F	154.4 ± 6.6	156.0 ± 6.0	0.091
Weight (kg)	M	64.7 ± 11.1	64.5 ± 9.9	0.952
	F	52.9 ± 9.3	52.8 ± 7.0	0.956
BMI (kg/m <sup>2</sup> )	M	23.2 ± 3.2	22.3 ± 2.8	0.29
	F	22.2 ± 3.8	22.2 ± 3.0	0.932
Rheumatoid factor positive, %	M	80.6	–	–
	F	89.1	–	–
Duration of RA (years)	M	7.8 ± 8.6	–	–
	F	11.4 ± 8.9	–	–
DAS28-ESR	M	3.4 ± 1.9	–	–
	F	3.8 ± 1.4	–	–
Stage of RA (I:II:III:IV)	M	12:5:6:8	–	–
	F	11:25:16:58	–	–
CRP (mg/L)	M	10.4 ± 10.5	–	–
	F	8.2 ± 14.4	–	–
ESR (mm/h)	M	23.7 ± 22.2	–	–
	F	33.6 ± 24.9	–	–

Data are shown as the mean±SD; M, Male; F, Female; RA, rheumatoid arthritis; BMI, body mass index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

**Table 2. Current Medications in Patients with Rheumatoid Arthritis**

Current medications	Male (n=31)			Female (n=110)		
	n	%	dosage	n	%	dosage
Prednisolone (mg/day)	10	32.3	4.4±2.6	52	47.2	5.2±2.1
Methotrexate (mg/week)	17	54.8	8.0±2.6	67	60.9	8.0±2.3
other DMARDs						
Salazosulfapyridine (g/day)	17	54.8	1.0±0.3	41	37.3	1.0±0.3
Bucillamine (mg/day)	11	35.5	132±64	19	17.3	192±42
Biological agents						
Infliximab (mg/kg/2 months)	1	3.2	3	8	7.3	3.7 ± 0.8
Etanercept (mg/week)	2	6.5	50	13	11.8	44 ± 11

Data are shown as the mean±SD; n, number of samples; DMARDs, disease modifying anti-rheumatic drugs

that adiponectin stimulates the production of IL-8 (6) and prostaglandin E<sub>2</sub> (7) by rheumatoid synovial fibroblasts. These findings suggest that adipokines may contribute to synovial inflammation in RA.

In the present study, we measured the serum concentrations of 3 adipokines (resistin, leptin, and adiponectin) in Japanese patients with RA and in normal controls to further investigate the role of these molecules in the pathogenesis of this disease.

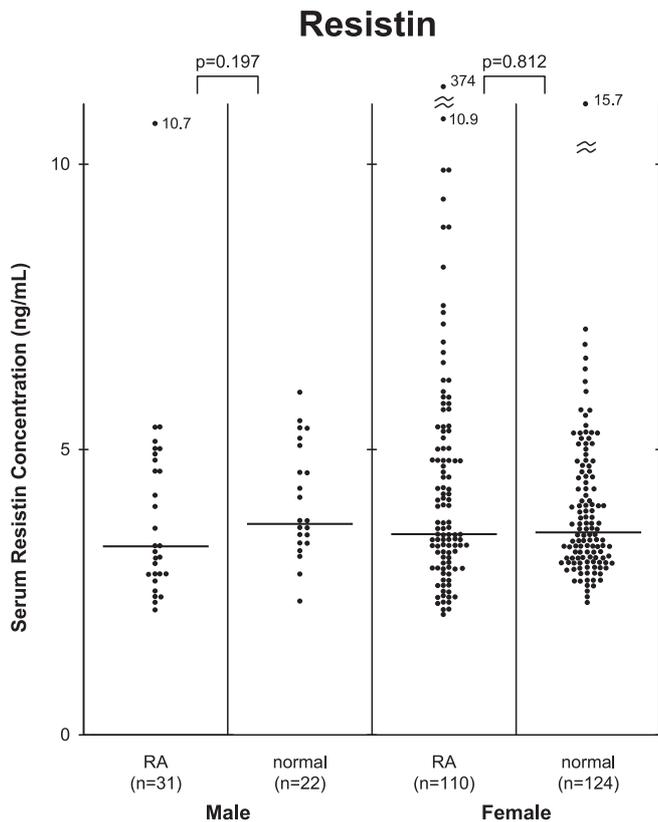
## Methods

### Subjects

One hundred and forty-one patients with RA diagnosed

according to 1987 revised criteria of the American Rheumatism Association (8) were enrolled in this study, and 146 healthy persons were also enrolled as controls. The demographic characteristics of the RA patients and the controls are shown separately for males and females in Table 1. Clinical features of the male and female RA patients are also shown in Table 1. The body mass index (BMI) was calculated as [body weight/height<sup>2</sup>] (kg/m<sup>2</sup>). Demographic characteristics did not differ between the RA group and the control group, except for the mean age of the males. Medications in the RA patients are shown in Table 2.

Disease activity score 28 (DAS28) was calculated with the following equation (9): DAS28 = 0.56 × √28TJC + 0.28 × √28SJC + 0.7 × ln ESR + 0.014 × GH, where 28TJC and 28SJC are the tender joint count and swollen



**Figure 1.** Serum resistin levels in RA patients and control subjects. Horizontal bars indicate median values. Statistical significance was determined by Mann-Whitney test.

joint count from 28 joints and general health (GH) is the patient's global assessment on a 100-mm visual analog scale (VAS).

This study was approved by the Ethical Committees of Toho University and Kitasato University. The RA patients and normal controls were recruited at Toho University Omori Hospital and the Research Center for Clinical Pharmacology of Kitasato University, respectively. Informed consent was obtained from both the patients and the normal controls. In all subjects, a blood sample was collected in the morning after an overnight fast. We did not provide any special dietary management information to the patients or normal controls.

#### Measurement of adipokines and other laboratory parameters

The serum concentrations of resistin, leptin, and adiponectin were measured by enzyme-linked immunosorbent assay (ELISA). Resistin and leptin ELISA kits were purchased from B-Bridge International, Inc. (Sunnyvale, CA, USA), while the kit for adiponectin was obtained from R&D Systems, Inc. (Minneapolis, MN, USA). Samples were prepared at the appropriate dilutions and paired samples were assayed together according to the instructions of the manufacturers. The intra- and inter-assay coefficients of variation for resistin, leptin, and adiponectin were: <4% and <7%, <8% and <10%, <5% and <7%, respectively. Rheuma-

toid factor was measured by nephelometry (Mitsubishi Kagaku Iatron, Tokyo, Japan). C-reactive protein (CRP) was also measured by nephelometry according to the manufacturer's specifications (Dade-Behring Inc., Deerfield, IL, USA). The erythrocyte sedimentation rate (ESR) was measured by the Westergren method.

#### Statistical analysis

Results are expressed as the mean and/or median. Statistical analysis was performed with StatFlex software (ver. 6; ARTEC Co., Ltd., Osaka, Japan). The significance of between-group differences in serum adipokine concentrations was determined by the Mann-Whitney non-parametric test, while differences of background data were evaluated by Student's *t*-test. Simple linear regression analysis was used to assess correlations between serum adipokine levels and patient characteristics, and stepwise forward multiple regression analysis was also performed. Logarithmic transformation was done for highly skewed variables (resistin, leptin, adiponectin, and CRP) when needed in order to satisfy the requirements of multivariate models. In all analyses,  $p < 0.05$  was considered to indicate statistical significance.

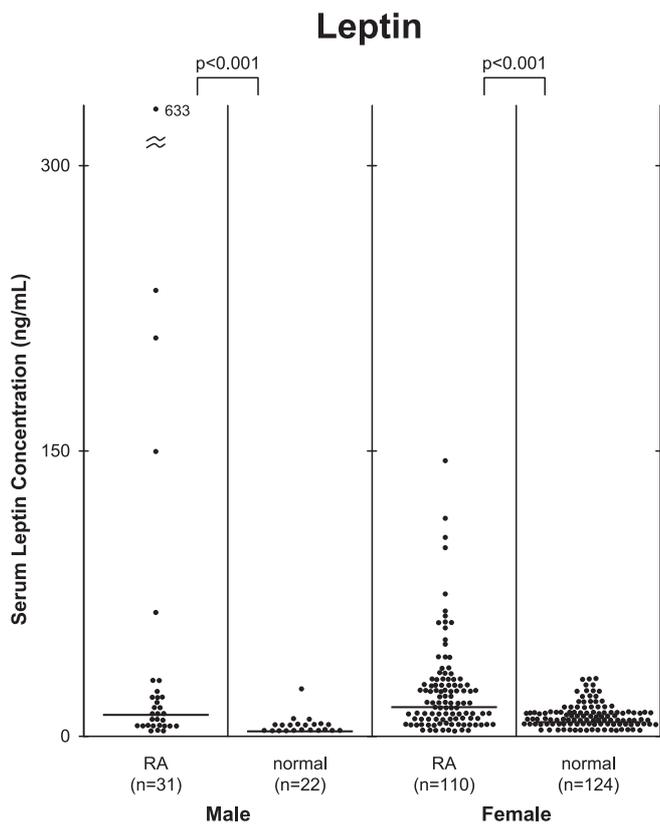
## Results

#### Serum adipokine concentrations

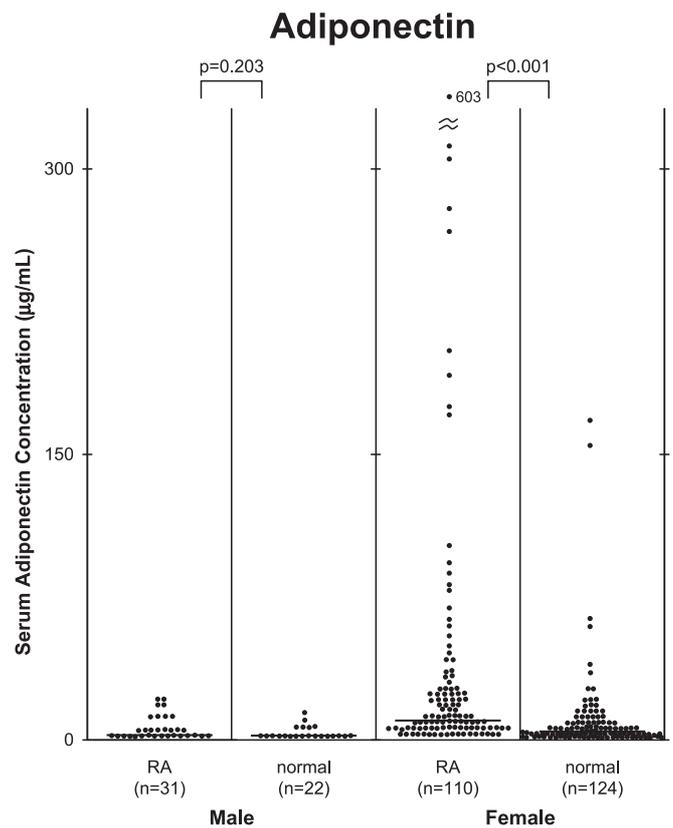
There were no statistically significant differences in serum resistin levels between the RA patients [males: 3.3 (2.8-4.9) ng/mL, females: 3.5 (2.5-5.0) ng/mL] and normal controls [males: 3.7 (3.4-5.0) ng/mL, females: 3.6 (3.1-4.5) ng/mL] (Fig. 1). However, the resistin levels of female RA patients were broadly distributed. Therefore, we compared CRP levels between patients with resistin levels above the 75th percentile (>4.95 ng/mL) and those with resistin levels below the 75th percentile. We found that the CRP level of the former subgroup was significantly higher than that of the latter subgroup ( $19.1 \pm 21.8$  mg/L vs.  $4.3 \pm 7.7$  mg/L,  $p < 0.001$ ).

The serum concentration of leptin was significantly ( $p < 0.001$ ) higher in male RA patients [median 11.2 (interquartile range, 5.1-20.3) ng/mL] than in normal male control subjects [2.7 (1.8-4.3) ng/mL], and serum leptin level was also significantly ( $p < 0.001$ ) higher in female RA patients [15.3 (7.3-26.7) ng/mL] than in normal female control subjects [7.4 (3.9-12.0) ng/mL] (Fig. 2). Serum leptin levels were significantly correlated with BMI in all subjects ( $p < 0.001$ ), except male RA patients ( $p = 0.955$ ), according to linear regression analysis. Since BMI is closely associated with the serum leptin concentration (10, 11), leptin levels were adjusted by BMI. As a result, the leptin/BMI ratios of RA patients [males: 0.51 (0.21-0.95), females: 0.69 (0.35-1.15)] were significantly ( $p < 0.001$ ) higher than those of normal control subjects [males: 0.12 (0.10-0.17), females: 0.33 (0.20-0.55)].

Female RA patients had significantly ( $p < 0.001$ ) higher serum adiponectin concentrations [10.1 (4.5-26.8)  $\mu$ g/mL] than



**Figure 2.** Serum leptin levels in RA patients and control subjects. Horizontal bars indicate median values. Statistical significance was determined by Mann-Whitney test.



**Figure 3.** Serum adiponectin levels in RA patients and control subjects. Horizontal bars indicate median values. Statistical significance was determined by Mann-Whitney test.

normal female control subjects [3.6 (2.4-7.4)  $\mu\text{g/mL}$ ], but no significant difference of adiponectin levels was observed in males (RA males: median 2.6  $\mu\text{g/mL}$ ; control males: median 2.3  $\mu\text{g/mL}$ ,  $p=0.203$ ) (Fig. 3).

#### **Correlations between adipokines and patient characteristics**

We included various patient characteristics [sex, age, BMI, duration of RA, stage, CRP, ESR, DAS28-ESR, prednisolone, methotrexate, other disease modifying anti-rheumatic drugs (DMARDs), and biological agents] in a model predicting the serum levels of adipokines (resistin, leptin, and adiponectin) (Table 3-5, respectively).

As shown in Table 3, significant univariate predictors of the serum level of resistin included age, BMI, CRP, ESR, and DAS28-ESR. Inclusion of these univariate predictors in a multivariate model resulted in the final selection of female sex and CRP as significant predictors (Table 3, multivariate model).

Significant univariate predictors of the leptin level included BMI, CRP, and DAS28-ESR (Table 4, univariate model), while multivariate analysis resulted in the final selection of BMI and CRP (Table 4, multivariate model).

For adiponectin, significant univariate predictors included female sex, BMI, RA stage, CRP, and current prednisolone use (Table 5, univariate model). On multivariate analysis, the significant predictors were reduced to CRP and current pred-

nisolone use (Table 5, multivariate model). In addition, a significant positive correlation was found between the serum adiponectin level and the dose of prednisolone in female RA patients by linear regression analysis ( $r=0.306$ ,  $p<0.05$ ). However, we did not find any significant correlation between serum adiponectin levels and the use of methotrexate and/or biological agents.

## **Discussion**

We measured the serum levels of 3 adipokines (resistin, leptin, and adiponectin) in 141 RA patients and 146 normal controls. Most of the previous studies showed the serum levels of several adipokines in only around 50 patients (12-24). They indicated that the serum resistin (12, 13, 25), leptin (14-16, 23, 25) and adiponectin (14, 22-25) levels are higher in RA patients than in healthy controls, while negative results (14, 17-20, 24) were also reported. The present results showed significantly elevated serum levels of leptin and adiponectin, and a trend for an elevated serum resistin level in RA patients. In addition, we found that the serum levels of resistin, leptin and adiponectin in the same samples were all associated with CRP, and they were individually associated with the different clinical conditions of female sex, BMI, and prednisolone use, respectively.

Some previous reports described that the serum levels of these adipokines were associated with dietary supple-

**Table 3. Crude and Adjusted Associations of the Serum Resistin Concentration and Patient Characteristics**

Characteristic	Resistin*						
	Univariate		R <sup>2</sup>	Multivariate (complex)		Multivariate (simplified)	
	β	p		β	p	β	p
Female	0.031	0.352	0.006	0.068	0.061	0.070	<u>0.027</u>
Age	0.004	<u>0.047</u>	0.028	0.002	0.259		
BMI	0.015	<u>0.041</u>	0.030	0.008	0.287		
RA duration	-0.005	0.082	0.022	-0.006	0.077		
Stage	0.029	0.227	0.010	0.022	0.441		
CRP*	0.083	<u>&lt;0.001</u>	0.150	0.075	<u>0.001</u>	0.086	<u>&lt;0.001</u>
ESR	0.004	<u>0.001</u>	0.080	0.001	0.556		
DAS28-ESR	0.043	<u>0.025</u>	0.037	-0.016	0.474		
Prednisolone	0.049	0.080	0.022	0.026	0.369		
Methotrexate	-0.002	0.938	0.000	-0.011	0.699		
Other DMARDs	0.017	0.563	0.002	0.023	0.428		
Biological agents	0.031	0.355	0.006	-0.004	0.911		
R <sup>2</sup>				0.163		0.173	

β: regression coefficient; DMARDs: disease modifying anti-rheumatic drugs; Other DMARDs: one or more of sulfasalazine, bucillamine, injectable gold, and/or auranofin; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index; R<sup>2</sup>: coefficient of determination.

\*Logarithmic transformation was done for highly skewed variables as needed to satisfy the requirements of multivariate models. Significant correlations (p<0.05) are underlined.

**Table 4. Crude and Adjusted Associations of the Serum Leptin Concentration and Patient Characteristics**

Characteristic	Leptin*						
	Univariate		R <sup>2</sup>	Multivariate (complex)		Multivariate (simplified)	
	β	p		β	p	β	p
Female	0.037	0.746	0.001	0.150	0.223		
Age	0.008	0.258	0.009	0.004	0.516		
BMI	0.113	<u>&lt;0.001</u>	0.138	0.103	<u>&lt;0.001</u>	0.104	<u>&lt;0.001</u>
RA duration	-0.005	0.621	0.002	-0.003	0.836		
Stage	0.130	0.111	0.018	0.079	0.411		
CRP*	0.216	<u>&lt;0.001</u>	0.087	0.185	<u>0.019</u>	0.187	<u>0.001</u>
ESR	0.004	0.287	0.008	-0.008	0.111		
DAS28-ESR	0.149	<u>0.022</u>	0.038	0.111	0.153		
Prednisolone	0.176	0.064	0.025	0.005	0.959		
Methotrexate	0.067	0.502	0.003	-0.045	0.642		
Other DMARDs	-0.008	0.933	<0.001	0.040	0.678		
Biological agents	0.149	0.186	0.013	0.090	0.500		
R <sup>2</sup>				0.162		0.187	

β: regression coefficient; DMARDs: disease modifying anti-rheumatic drugs; Other DMARDs: one or more of sulfasalazine, bucillamine, injectable gold, and/or auranofin; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index; R<sup>2</sup>: coefficient of determination.

\*Logarithmic transformation was done for highly skewed variables as needed to satisfy the requirements of multivariate models. Significant correlations (p<0.05) are underlined.

ments (26-28). The present study did not investigate the relationship between the serum adipokine levels and dietary supplements; no special dietary management was provided for the patients or normal controls.

Tarkowski et al (29) demonstrated that resistin competes with lipopolysaccharide for binding to Toll-like receptor-4 and may act as a pro-inflammatory cytokine in human monocytes. In the present study, we found that the CRP level was higher in the subgroup of high serum resistin levels than in the subgroup of low serum resistin levels. In addition, the CRP level was a significant predictor of the higher serum resistin level according to multivariate analy-

sis. These data suggest that an increased serum level of resistin may contribute to inflammation in RA patients. However, the reason for the gender difference, in which the female sex was associated with high serum resistin levels, is unknown.

Simons et al (30) described that TNFα and IL-1β stimulate leptin production by human preadipocytes. Some reports have described a significant positive correlation between the serum leptin level and the disease activity of RA (14, 15, 21). We also found a significant correlation between the serum leptin level and CRP by multivariate analysis in this study.

**Table 5. Crude and Adjusted Associations of the Serum Adiponectin Concentration and Patient Characteristics**

Characteristic	Adiponectin*						
	Univariate		R <sup>2</sup>	Multivariate (complex)		Multivariate (simplified)	
	$\beta$	p		$\beta$	p	$\beta$	p
Female	0.654	<0.001	0.152	7.676	0.370		
Age	0.011	0.191	0.012	0.891	0.065		
BMI	-0.068	<u>0.034</u>	0.032	-2.626	0.139		
RA duration	0.025	0.061	0.025	-0.538	0.515		
Stage	0.294	<u>0.003</u>	0.060	3.774	0.572		
CRP*	-0.175	<u>0.024</u>	0.037	-11.144	<u>0.042</u>	-10.453	<u>0.010</u>
ESR	-0.106	0.678	0.001	-0.120	0.728		
DAS28-ESR	0.025	0.755	0.001	4.106	0.448		
Prednisolone	0.283	<u>0.016</u>	0.041	15.485	<u>0.023</u>	17.594	<u>0.005</u>
Methotrexate	0.070	0.572	0.002	-0.428	0.949		
Other DMARDs	-0.061	0.629	0.000	-1.853	0.786		
Biological agents	0.095	0.499	0.003	0.427	0.963		
R <sup>2</sup>				0.055		0.090	

$\beta$ : regression coefficient; DMARDs: disease modifying anti-rheumatic drugs; Other DMARDs: one or more of sulfasalazine, bucillamine, injectable gold, and/or auranofin; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BMI: body mass index; R<sup>2</sup>: coefficient of determination.

\*Logarithmic transformation was done for highly skewed variables as needed to satisfy the requirements of multivariate models. Significant correlations (p<0.05) are underlined.

Previous reports have shown that the serum leptin level is positively correlated with BMI, (10, 11) as observed in this study, except for male RA patients. We also found that leptin/BMI ratio of RA patients was significantly higher than that of normal control subjects. Based on these results, the absence of correlation between the serum leptin level and BMI in male RA patients might be explained by the influence of inflammation. Moreover, it was suggested that leptin may act as a pro-inflammatory cytokine in this disease.

Rho et al (25) suggested that leptin was associated with reduced radiographic joint damage as estimated by the Larsen score (31). In the present study, leptin as well as other adipokines were not associated with the Steinbrocker stage of RA. In general, high disease activity in RA patient is correlated with joint damage. The relationship between the serum leptin level and radiographic joint damage should be studied in the future.

The serum adiponectin level was significantly higher in female RA patients than in normal female controls. We also found the same trend in male RA patients, although the difference was not statistically significant. However, the serum CRP level was negatively associated with the adiponectin level in RA patients. Schäffler et al (32) reported that adiponectin was increased in the synovial fluid of RA patients compared with osteoarthritis patients, but they found no statistically significant correlations between adiponectin and ESR or CRP in RA patients. Our previous *in vitro* studies (6, 7) have suggested that adiponectin might be a pro-inflammatory cytokine for rheumatoid synovial fibroblasts. The discrepancies in the adiponectin studies between *in vitro* pro-inflammatory effects and various facets in clinical inflammatory conditions in RA patients remain to be studied.

In the present study, the serum adiponectin level was sig-

nificantly correlated with current prednisolone use by multiple regression analysis, and was also significantly correlated with the dose of prednisolone by linear regression analysis. Maeda et al (33) reported the reciprocal suppression of adiponectin and TNF $\alpha$  production in adipose tissue. Corticosteroids inhibit the production of pro-inflammatory cytokines such as TNF $\alpha$  (34). Thus, the reduction of TNF $\alpha$  by prednisolone might be the cause of the increased serum adiponectin level in the present RA patients.

Laurberg et al (35) found that the plasma adiponectin level was increased by 13% in RA patients who received methotrexate treatment. Nishida et al (36) reported that serum adiponectin levels showed an increase during infliximab (TNF $\alpha$  inhibitor) therapy in RA patients. However, we did not find significant correlations between serum adiponectin levels and the use of methotrexate and/or biological agents in the present study. The reason for the absence of correlation between serum adiponectin levels and TNF $\alpha$  inhibitor therapy might be explained by the small number of patients receiving TNF $\alpha$  inhibitors, comparing with those receiving prednisolone.

In summary, the serum levels of resistin and leptin were positively associated with CRP level in patients with rheumatoid arthritis, suggesting that these adipokines may act as pro-inflammatory cytokines in this disease. The serum adiponectin level was elevated in the patients, however, it was negatively associated with CRP level. In addition, the serum levels of resistin, leptin, and adiponectin were also associated with female sex, BMI and the use of prednisolone, respectively.

**The authors state that they have no Conflict of Interest (COI).**

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