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

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Abstract

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

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- α (TNF α), 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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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 ²) | 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 | | | | | | |
| Salazosulapyridine (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 E₂ (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/height²] (kg/m²). 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

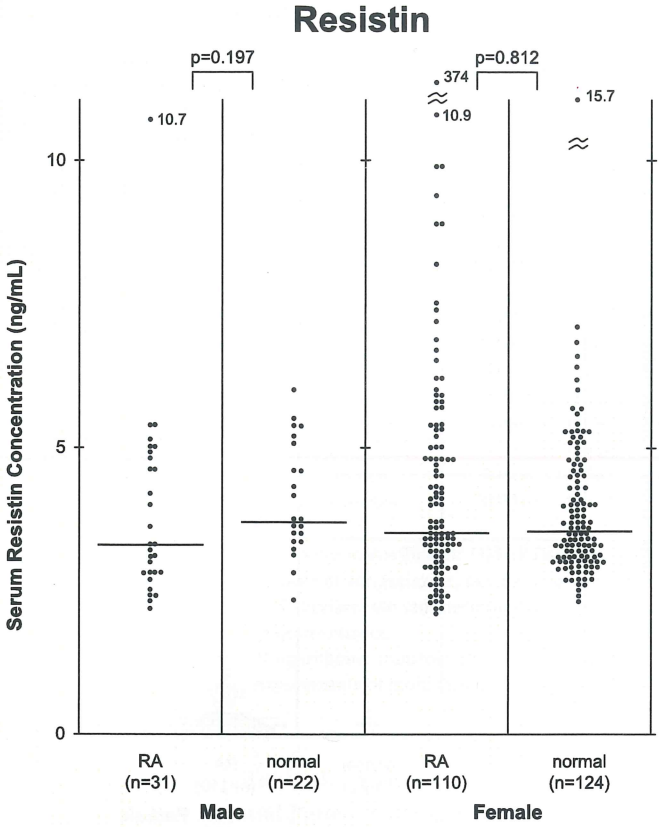


Figure 1. Serum resistin levels in RA patients and control subjects. Horizontal bars indicate median values. Statistical significance was determined by Mann-Whitney test.

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±21.8 mg/L vs. 4.3±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) μg/mL] than

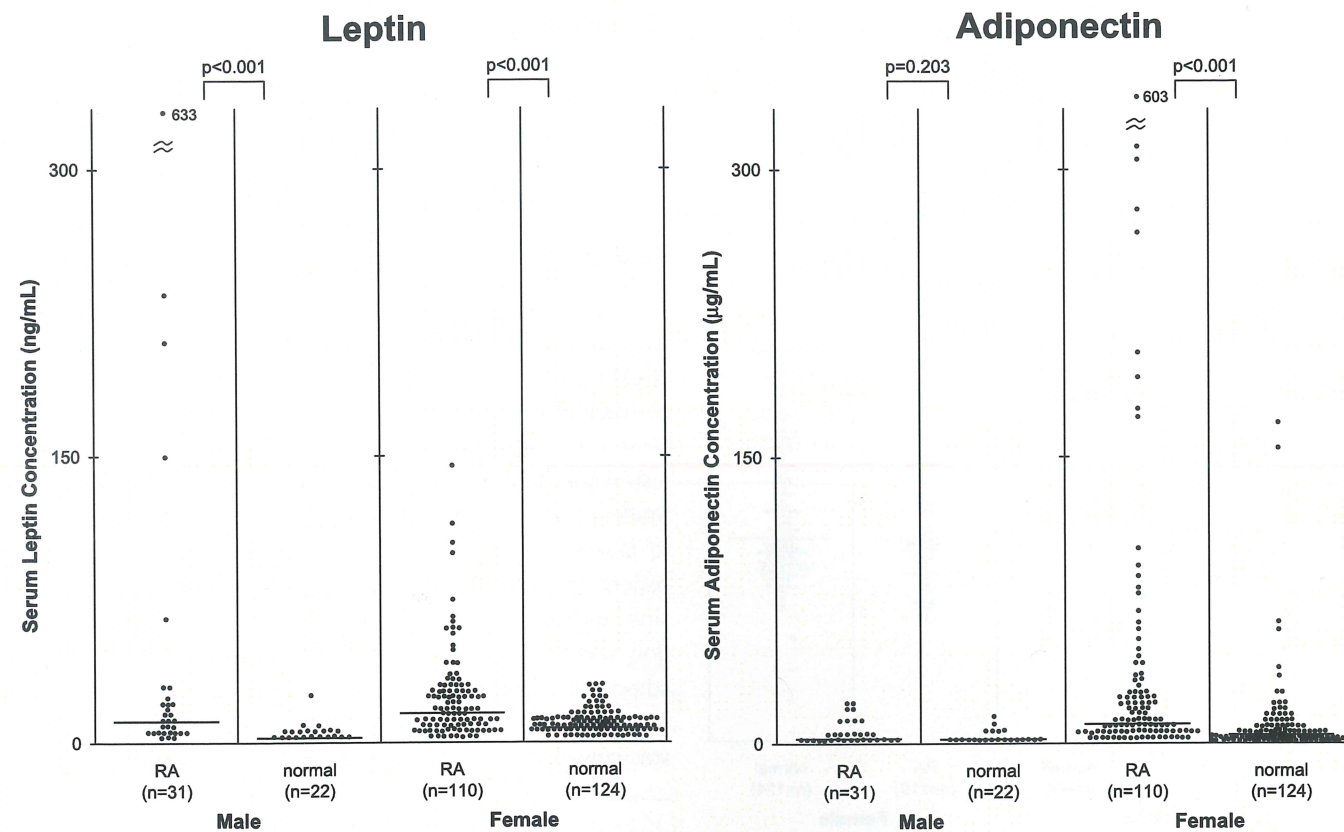


Figure 2. Serum leptin levels in RA patients and control subjects. Horizontal bars indicate median values. Statistical significance was determined by Mann-Whitney test.

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-

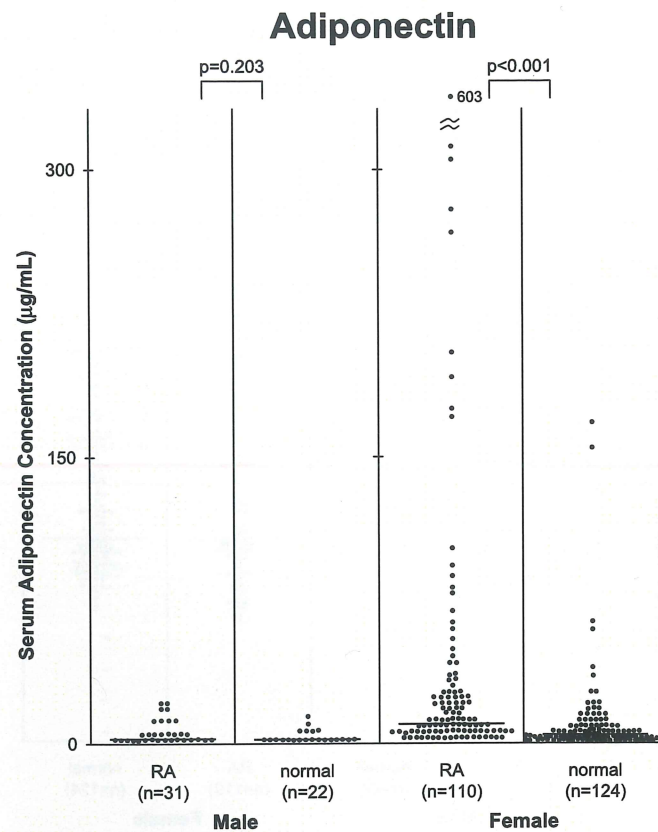


Figure 3. Serum adiponectin levels in RA patients and control subjects. Horizontal bars indicate median values. Statistical significance was determined by Mann-Whitney test.

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 ² | Multivariate (complex) | | Multivariate (simplified) | |
| | β | p | | β | p | β | p |
| Female | 0.031 | 0.352 | 0.006 | 0.068 | 0.061 | 0.070 | 0.027 |
| Age | 0.004 | 0.047 | 0.028 | 0.002 | 0.259 | | |
| BMI | 0.015 | 0.041 | 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 | <0.001 | 0.150 | 0.075 | 0.001 | 0.086 | <0.001 |
| ESR | 0.004 | 0.001 | 0.080 | 0.001 | 0.556 | | |
| DAS28-ESR | 0.043 | 0.025 | 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 ² | | | | 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; R²: 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 ² | 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 | <0.001 | 0.138 | 0.103 | <0.001 | 0.104 | <0.001 |
| 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 | <0.001 | 0.087 | 0.185 | 0.019 | 0.187 | 0.001 |
| ESR | 0.004 | 0.287 | 0.008 | -0.008 | 0.111 | | |
| DAS28-ESR | 0.149 | 0.022 | 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 ² | | | | 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; R²: 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 TNF α and IL-1 β 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 ² | Multivariate (complex) | | Multivariate (simplified) |
| | β | p | | β | p | β p |
| Female | 0.654 | <u><0.001</u> | 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 ² | | | | 0.055 | | 0.090 |

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; R²: 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 TNFα production in adipose tissue. Corticosteroids inhibit the production of pro-inflammatory cytokines such as TNFα (34). Thus, the reduction of TNFα 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 (TNFα 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 TNFα inhibitor therapy might be explained by the small number of patients receiving TNFα 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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References

1. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet* **370**: 1861-1874, 2007.

2. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature* **423**: 356-361, 2003.

3. Arend WP. Physiology of cytokine pathways in rheumatoid arthritis. *Arthritis Rheum* **45**: 101-106, 2001.

4. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* **6**: 772-783, 2006.

5. Koerner A, Kratzsch J, Kiess W. Adipocytokines: leptin--the classical, resistin--the controversial, adiponectin--the promising, and more to come. *Best Pract Res Clin Endocrinol Metab* **19**: 525-546, 2005.

6. Kitahara K, Kusunoki N, Kakiuchi T, Suguro T, Kawai S. Adiponectin stimulates IL-8 production by rheumatoid synovial fibroblasts. *Biochem Biophys Res Commun* **378**: 218-223, 2009.

7. Kusunoki N, Kitahara K, Kojima F, et al. Adiponectin stimulates prostaglandin E₂ production in rheumatoid synovial fibroblasts. *Arthritis Rheum* **62**: 1641-1649, 2010.

8. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* **31**: 315-324, 1988.

9. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* **23**: S93-S99, 2005.

10. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and *ob* RNA in obese and weight-reduced subjects. *Nat Med* **1**: 1155-1161, 1995.

11. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive leptin concentrations in normal-weight and obese humans. *N Engl J Med* **334**: 292-295, 1996.

12. Migita K, Maeda Y, Miyashita T, et al. The serum levels of resistin in rheumatoid arthritis patients. *Clin Exp Rheumatol* **24**: 698-701, 2006.

13. Šenolt L, Housa D, Vernerová Z, et al. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* **66**: 458-463, 2007.

14. Otero M, Lago R, Gomez R, et al. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* **65**: 1198-1201, 2006.

15. Targońska-Stepniak B, Majdan M, Dryglewska M. Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. *Rheumatol Int* **28**: 585-591, 2008.

16. Gunaydin R, Kaya T, Atay A, Olmez N, Hur A, Koseoglu M. Serum leptin levels in the rheumatoid arthritis and relationship with disease activity. *South Med J* **99**: 1078-1083, 2006.

17. Hizmetli S, Kisa M, Gokalp N, Bakici MZ. Are plasma and synovial fluid leptin levels correlated with disease activity in rheumatoid arthritis? *Rheumatol Int* **27**: 335-338, 2007.

18. Anders HJ, Rihl M, Heufelder A, Loch O, Schattenkirchner M. Leptin serum levels are not correlated with disease activity in pa-

tients with rheumatoid arthritis. *Metabolism* **48**: 745-748, 1999.

19. Wiśłowska M, Rok M, Jaszczuk B, Stepień K, Cicha M. Serum leptin in rheumatoid arthritis. *Rheumatol Int* **27**: 947-954, 2007.

20. Popa C, Netea MG, Radstake TR, van Riel PL, Barrera P, van der Meer JW. Markers of inflammation are negatively correlated with serum leptin in rheumatoid arthritis. *Ann Rheum Dis* **64**: 1195-1198, 2005.

21. Lee SW, Park MC, Park YB, Lee SK. Measurement of the serum leptin level could assist disease activity monitoring in rheumatoid arthritis. *Rheumatol Int* **27**: 537-540, 2007.

22. Šenolt L, Pavelka K, Housa D, Haluzík M. Increased adiponectin is negatively linked to the local inflammatory process in patients with rheumatoid arthritis. *Cytokine* **35**: 247-252, 2006.

23. Härle P, Sarzi-Puttini P, Cutolo M, Straub RH. No change of serum levels of leptin and adiponectin during anti-tumour necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis* **65**: 970-971, 2006.

24. Popa C, Netea MG, de Graaf J, et al. Circulating leptin and adiponectin concentrations during tumor necrosis factor blockade in patients with active rheumatoid arthritis. *J Rheumatol* **36**: 724-730, 2009.

25. Rho YH, Solus J, Sokka T, et al. Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. *Arthritis Rheum* **60**: 1906-1914, 2009.

26. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu Rev Nutr* **30**: 173-199, 2010.

27. Zhao WS, Zhai JJ, Wang YH, et al. Conjugated linoleic acid supplementation enhances antihypertensive effect of ramipril in Chinese patients with obesity-related hypertension. *Am J Hypertens* **22**: 680-686, 2009.

28. Nelson TL, Stevens JR, Hickey MS. Adiponectin levels are reduced, independent of polymorphisms in the adiponectin gene, after supplementation with alpha-linolenic acid among healthy adults. *Metabolism* **56**: 1209-1215, 2007.

29. Tarkowski A, Bjersing J, Shestakov A, Bokarewa MI. Resistin competes with lipopolysaccharide for binding to Toll-like receptor 4. *J Cell Mol Med* **14**: 1419-1431, 2010.

30. Simons PJ, van den Pangaart PS, van Roomen CP, Aerts JM, Boon L. Cytokine-mediated modulation of leptin and adiponectin secretion during *in vitro* adipogenesis: evidence that tumor necrosis factor-α and interleukin-1β-treated human preadipocytes are potent leptin producers. *Cytokine* **32**: 94-103, 2005.

31. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diagn (Stockh)* **18**: 481-491, 1977.

32. Schäffler A, Ehling A, Neumann E, et al. Adipocytokines in synovial fluid. *JAMA* **290**: 1709-1710, 2003.

33. Maeda N, Shimomura I, Kishida K, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* **8**: 731-737, 2002.

34. Smoak K, Cidlowski JA. Glucocorticoids regulate tristetraproline synthesis and posttranscriptionally regulate tumor necrosis factor α inflammatory signaling. *Mol Cell Biol* **26**: 9126-9135, 2006.

35. Laurberg TB, Frystyk J, Ellingsen T, et al. Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naïve compared with patients with osteoarthritis and controls. *J Rheumatol* **36**: 1885-1891, 2009.

36. Nishida K, Okada Y, Nawata M, Saito K, Tanaka Y. Induction of hyperadiponectinemia following long-term treatment of patients with rheumatoid arthritis with infliximab (IFX), an anti-TNF-α antibody. *Endocr J* **55**: 213-216, 2008.