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Adipocytokines Are Associated with Radiographic Joint Damage in Rheumatoid Arthritis

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Abstract

Objectives—Obesity protects against radiographic joint damage in rheumatoid arthritis (RA) through poorly defined mechanisms. Adipocytokines are produced in adipose tissue and modulate inflammatory responses and joint damage in animal models. We examined the hypothesis that adipocytokines modulate inflammation and joint damage in patients with RA.

Methods—We compared serum concentrations of leptin, resistin, adiponectin and visfatin in 167 patients with RA and 91 control subjects. The independent association between adipocytokines and body mass index (BMI), measures of inflammation (C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)) and radiographic damage (Larsen score, n=93) was examined in patients with RA with multivariable regression analysis first controlling for age, race and sex, and then obesity (BMI) and inflammation (TNF- α , IL-6 and CRP).

Results—Concentrations of all adipocytokines were significantly higher in RA than controls (all $p < 0.01$); for visfatin ($p < 0.001$) and adiponectin ($p < 0.05$) this association remained significant after adjusting for BMI, inflammation, or both. Visfatin concentrations were associated with higher Larsen score and this remained significant after adjustment for age, race, sex, disease duration, BMI and inflammation (OR=2.38, 95%CI: 1.32–4.29, $p = 0.004$). Leptin concentrations were associated positively with BMI ($\rho = 0.58$, $p < 0.01$) and negatively with Larsen score after adjustment for inflammation (OR=0.32, 95%CI: 0.17–0.61, $p < 0.001$) but not after adjustment for BMI (OR 0.86, 95%CI: 0.42–1.73, $p = 0.67$).

Conclusions—Concentrations of adipocytokines are increased in patients with RA and may modulate radiographic joint damage. Visfatin is associated with increased, and leptin with reduced radiographic joint damage.

Keywords

Rheumatoid Arthritis; Adipocytokine; Visfatin; Leptin; Resistin; Adiponectin; Larsen Score; Obesity

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Introduction

Obesity is consistently associated with reduced radiographic joint damage in patients with rheumatoid arthritis (RA)(1-3), but the mechanisms underlying these observations are not known. Adipose tissue is a source of inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6)(4), and obesity is associated with a chronic inflammatory response. Therefore, the association between obesity and reduced radiographic joint damage appears paradoxical.

Adipose tissue is also a major source of several mediators termed adipocytokines that include leptin, resistin, adiponectin and visfatin. They have profound effects not only on glucose homeostasis and appetite regulation, but also on inflammation(4). For example, leptin, resistin and visfatin are pro-inflammatory(4), whereas adiponectin is anti-inflammatory(5). Adipocytokines have diverse immunological effects. Leptin, best known for its ability to regulate body weight by decreasing food intake and increasing energy expenditure, also has immunomodulatory effects. Leptin production is stimulated by inflammation and it is pro-inflammatory, inducing T-cell activation and production of inflammatory mediators such as TNF- α , IL-6 and nitric oxide(4,6). Adiponectin transcription, on the other hand, is suppressed by inflammatory cytokines such as TNF- α and IL-6 (4). Resistin, also known as FIZZ3 (found in inflammatory zone 3)(7), induces TNF- α and IL-6(8). Visfatin(9), also known as pre-B cell colony-enhancing factor (PBEF) (10) or nicotinamide phosphoribosyl transferase (NAMPT)(11), is produced by visceral adipose tissue and also by other cells such as macrophages and neutrophils. It is induced by inflammation and immune activation(12) and has immunomodulatory properties including enhancement of B cell differentiation, induction of cytokines and matrix metalloproteinases(13), and inhibition of apoptosis(14).

Concentrations of adipocytokines have generally been reported to be higher in patients with RA than control subjects(15-17). However, information regarding their relationship with inflammation and disease activity is conflicting(18,19), and little is known about their role in radiographic joint damage. We examined the hypothesis that adipocytokines may affect inflammation and disease activity in RA and contribute to reduced joint damage in obesity.

Materials and Methods

Patients and Control Subjects

We studied 167 patients with RA and 91 control subjects frequency-matched for age, race and sex through advertisements, referral from local rheumatologists, or from a volunteer database maintained by the General Clinical Research Center (GCRC) at Vanderbilt University. Subjects were older than 18 years and patients with RA fulfilled the ACR classification criteria(20). The study sample was selected to be enriched with patients with relatively early RA or established disease. Control subjects did not meet the classification criteria for RA and had no inflammatory disease. These subjects are part of an ongoing study and enrollment procedures have previously been described in detail(21). This study was approved by the Vanderbilt University Institutional Review Board and all subjects gave written informed consent.

Clinical and Laboratory Measurements

Clinical information and laboratory data were obtained through a structured interview, self-reported questionnaires, physical examination and blood tests. The degree of obesity was measured using the body mass index (BMI) as kg/m². Disease activity was measured using the disease activity score using 28 joints (DAS28)(22). Functional capacity was measured

using the modified health assessment questionnaire (MHAQ)(23), a standard 8-question instrument addressing activities of daily living.

Radiographs of the hands and feet were available for 93 patients. These had been obtained at a median of 1.9 (IQR [1.1–2.7]) years before the date of enrollment to this study. A single investigator (TS) who was blinded to the adipocytokine concentrations determined radiographic damage using the Larsen score, a standardized method for quantifying the amount of damage of the joints of the hands, wrists and feet(24,25). Twenty joints were evaluated: the wrists, 1st to 5th metacarpophalangeal joints, and 2nd to 5th metatarsophalangeal joints, with a total score ranging from 0 to 100.

C-reactive protein (CRP) and rheumatoid factor (RF, n=159) were measured by the Vanderbilt University Medical Center Clinical Laboratory. Serum concentrations of TNF- α , IL-6, leptin, resistin, and adiponectin were measured by multiplex ELISA (Lincoplex[®] Multiplex Immunoassay Kit, Linco Research, St. Charles, MO, USA). Visfatin was measured by Visfatin C-terminal ELISA kit (Phoenix Pharmaceuticals, Inc, Burlingame, CA, USA).

Statistical Analysis

Descriptive statistics were calculated as mean $\pm$ standard deviation (SD) or median [interquartile range (IQR)] according to distributions of continuous variables. Concentrations of each adipocytokine were compared in patients with RA and control subjects, and then in patients with RA who were seropositive (RF-positive) and seronegative (RF-negative) using Wilcoxon rank-sum tests. We assessed the relationship between adipocytokines and obesity (BMI), disease activity and damage (DAS28, MHAQ and Larsen scores) and inflammation (TNF- α , IL-6 and CRP) using Spearman's rank correlation test.

The association between RA and each adipocytokine was assessed using linear regression models with concentrations of each adipocytokine as the outcome variable and disease status (RA or control) as the predictor variable. Since adipocytokines are associated with both obesity and inflammation, we defined four models *a priori* in order to examine the contribution of each component separately and in combination. The base model was adjusted for age, sex, and race. In addition to the base model we controlled for obesity (base +BMI) and inflammation (base+ TNF- α , IL-6, and CRP) separately, and in combination (full model; base+BMI+inflammation). With logarithmic (log10) transformation of the outcome variable (adipocytokine concentration) the exponentiated regression coefficient (10^b) for disease status can be interpreted as the average value of the serum adipocytokine concentration among RA relative to that of controls. For example, $10^b=1.2$ indicates a 20% increase in mean serum adipocytokine concentration among patients with RA compared to controls.

The association between adipocytokines and Larsen score was tested by applying a proportional odds logistic regression (POR) model because the Larsen score was heavily skewed. The approach for controlling for confounders was similar to the model described above, using the same four approaches (base model, base+BMI, base+inflammation, base +BMI+ inflammation; however, since disease duration is a strong predictor of Larsen score(26), it was included in the base model for these analyses. For all models each adipocytokine was logarithm-transformed to ensure linearity and to stabilize variance. The effect sizes were shown as odds ratios (OR) per IQR difference with 95% confidence intervals (95% CI). Additional sensitivity analyses were performed to assess the effect of adipocytokines on Larsen score among RA patients with inclusion of a further set of *a priori* selected factors known to be associated with Larsen score. Covariates included the time between the date of enrollment and the radiograph, smoking, DAS28, MHAQ, RF status and

duration of corticosteroid, methotrexate, leflunomide, hydroxychloroquine and TNF- α inhibitor exposure. Data reduction applying principal components of correlated variables for inflammations markers, medication use and disease severity were used to minimize over-fitting of the model. The distribution of variables in patients with and without Larsen scores available was compared using Wilcoxon rank-sum test for continuous and chi-square test for categorical variables.

Statistical significance was determined using a two-sided 5% significance level (p value <0.05). Statistical analysis was done with R 2.6.2 (<http://www.r-project.org>).

Results

The characteristics of patients with RA and control subjects and the concentrations of adipocytokines in the two groups are shown in Table 1. Concentrations of leptin, resistin, adiponectin and visfatin were significantly higher in patients with RA than in control subjects. In patients with RA, leptin concentrations were lower in smokers than non-smokers ($P=0.009$) but concentrations of other adipocytokines and DAS28 and Larsen scores did not differ significantly between smokers and non-smokers (all P values > 0.05). Visfatin concentrations were significantly higher in patients with seropositive RA ($n=114$; 6.4 [5.2–9.3] ng/ml) compared to seronegative RA ($n=45$; 5.3 [3.8–7.0] ng/ml) ($p<0.001$). Concentrations of leptin, resistin and adiponectin did not differ significantly among patients with seropositive and seronegative RA.

When only considering the patients who had radiographs available, the median disease duration at the time when blood was drawn was 5.0 years (IQR [2.0–20.0]) and at the time of X-ray was 2.7 years (IQR[0.58–17.9]) The clinical characteristics in the 93 patients in whom radiographs were available are shown in Table 2 according to whether patients had evidence of radiological changes (Larsen score >0) or not (Larsen score=0). Patients with radiological changes were older and had longer disease duration and higher concentrations of IL-6 and visfatin.

The Spearman correlations between adipocytokines, BMI and measures of inflammation and disease activity are shown in Table 3. BMI correlated positively with leptin and negatively with adiponectin but was not correlated with resistin and visfatin. Consistent with the univariate correlations with BMI as a continuous variable, when patients with RA were categorized into BMI categories of normal ($BMI < 25 \text{ kg/m}^2$, $n=54$), overweight ($25 \leq BMI < 30 \text{ kg/m}^2$, $n=42$) and obese ($BMI \geq 30 \text{ kg/m}^2$, $n=71$), leptin concentration was significantly associated with higher, and adiponectin with lower BMI (both $P < 0.001$, Kruskal-Wallis test). Resistin and visfatin concentrations did not differ significantly across BMI categories.

Disease duration correlated significantly with adiponectin and visfatin concentrations. As regards inflammatory mediators and RA disease indices (Table 3), the most striking associations were observed with visfatin which was positively correlated with TNF- α , IL-6, CRP, neutrophil count, MHAQ score and Larsen score. Leptin was positively correlated with DAS28, IL-6 and CRP. As expected, adiponectin and leptin were significantly inversely correlated ($\rho = -0.20$, $p=0.01$), but there were no statistically significant correlations between the other adipocytokines ($p>0.05$).

Analyses performed to examine whether higher concentrations of individual adipocytokines associated with RA were accounted for by BMI or inflammation are shown in Figure 1. Visfatin and adiponectin remained significantly higher in RA after adjustment for age, race and sex (base model), and also after additional adjustment for BMI, inflammation, or both. The higher leptin concentrations in RA remained statistically significant after adjustment for

BMI, but not after adjustment for inflammation, or both BMI and inflammation. Resistin was significantly higher in RA in the base model and after additional adjustment for BMI, but not after adjustment for inflammation, or both BMI and inflammation.

The associations between Larsen score and adipocytokines are shown in Figure 2. Visfatin was consistently associated with a higher Larsen score across all 4 models (base, base+BMI, base+inflammation and base+BMI+inflammation) with an OR of 2.38, 95%CI: 1.32–4.29 ($p=0.004$) for the full model (i.e. base+BMI+inflammation). In contrast, leptin was marginally associated with a lower Larsen score (base model OR=0.58, 95%CI: 0.33–1.01; $p=0.05$). This relationship was not significant after adjustment for BMI (OR=0.86, 95%CI: 0.42–1.73; $p=0.67$), but was stronger after adjustment for inflammation (OR=0.32, 95%CI: 0.17–0.61; $p<0.001$). This negative relationship was attenuated when both BMI and inflammation were included in the model (OR=0.45, 95%CI: 0.21–0.98; $p=0.04$). Resistin was weakly associated with higher Larsen score (OR=1.71, 95%CI: 1.04–2.80; $p=0.03$), and the association was maintained after adjustment for BMI ($p=0.02$) and attenuated by adjustment for inflammation ($p=0.07$) and in the fully adjusted model ($p=0.06$). Adiponectin was marginally associated with higher Larsen score ($p=0.05$, base model) and this was attenuated by adjustments that included BMI ($p=0.24$, BMI model; $p=0.67$, full model).

In a separate analysis, the relationship between BMI and Larsen score was examined. Consistent with previous studies, BMI was significantly associated with a lower Larsen score (OR=0.39, 95%CI 0.18–0.84; $p=0.02$, adjusted for age, race, sex and disease duration) and also after additional adjustment for inflammation (OR=0.27, 95%CI 0.12–0.61; $p=0.002$). Patients in whom radiographs were (n=93) or were not (n=74) available for determination of Larsen score did not differ significantly with regard to race, sex, current smoking, disease duration, RF seropositivity, MHAQ and DAS28 score (all $p>0.05$). Patients with radiographs tended to have a lower median BMI (27.3 kg/m² vs. 29.3 kg/m², $p=0.002$) and to be older (median age 55.0 years vs. 52.0 years, $p=0.047$).

A sensitivity analysis that included many factors additional to age, race, sex, BMI inflammation, and disease duration that could affect the Larsen score (the time between the date of enrollment and radiograph, smoking, DAS28, MHAQ, RF status and duration of corticosteroid, methotrexate, hydroxychloroquine, leflunomide and TNF- α inhibitor exposure) yielded almost identical findings. Visfatin was significantly associated with a higher Larsen score ($p=0.005$), while leptin was marginally associated with a lower Larsen score ($p=0.045$) and this association was more significant when BMI was not included in the model ($p=0.001$), consistent with the primary analysis. Adiponectin was not associated with Larsen score ($p=0.5$), while resistin was marginally associated ($p=0.07$), again consistent with the primary analysis.

Discussion

This study has several important findings. First, visfatin concentrations were elevated in patients with RA and associated with increased radiographic joint damage, independent of obesity and measures of inflammation. Second, leptin concentrations were higher in RA independent of BMI, and were associated with reduced radiographic joint damage, particularly after adjustment for inflammation.

Although visfatin is an adipocytokine, concentrations have generally not been found to be related to obesity(27,28), but rather have been associated with inflammatory markers in some studies in the general population(4,29). Visfatin concentrations were increased in several small studies of patients with RA(12,13,16), and it is also present in synovial fluid and tissue(12,13). We found that visfatin concentrations were higher in patients with RA

than controls and correlated with inflammatory mediators. Notably, visfatin concentrations remained significantly higher in patients with RA after adjustment for BMI and measures of inflammation (TNF- α , IL-6 and CRP), suggesting that visfatin may be independently associated with RA.

Visfatin expression is increased in rheumatoid synovial fibroblasts, particularly at sites of invasion of cartilage(13). Our observation that visfatin was associated with radiographic joint damage provides further evidence that it may be a mediator of joint damage. Indeed, a recent study(30) identified visfatin as a key component of a newly described inflammatory pathway leading to arthritis showing that an inhibitor of visfatin reduced inflammation, arthritis severity and cartilage damage markedly in a collagen-induced arthritis model. Visfatin mediates the rate limiting step in the salvage pathway that forms nicotinamide adenine dinucleotide (NAD) from nicotinamide(29). Pharmacological inhibition of visfatin led to reduced intracellular NAD in inflammatory cells and decreased production of TNF- α and IL-6 with clinical effects comparable to those of a TNF- α inhibitor in a murine arthritis model(30). Thus, taken together, these findings suggest visfatin may be an independent contributor to the pathogenesis of RA and associated joint damage, and may represent a novel therapeutic target.

As has been the case in some(16·17·31) but not all studies in RA(18·19·32·33), leptin concentrations were higher in patients with RA and were associated with some measures of inflammation. The association between increased concentrations of leptin and RA was not affected by statistical adjustment for BMI, but after adjustment for inflammation it was no longer significant. Thus, the higher concentrations of leptin in patients with RA than controls can be attributed to differences in inflammation rather than BMI. In addition to its association with inflammation, leptin may also modulate joint damage.

Considering that obesity, despite inducing low grade inflammation, is associated with reduced radiographic joint damage in RA(1-3), it is particularly important to define the potential role of the adipocytokines most closely associated with obesity, leptin and adiponectin. In one study(34), serum leptin concentrations were higher in patients with erosive RA. Another study has shown concentrations of leptin in synovial fluid were lower than those in plasma in patients with non-erosive RA, but not in those with erosive disease(31). This was thought to indicate that consumption of leptin in the joint was associated with protection against erosions, and therefore that leptin protected against bone erosions(31). We found that higher serum leptin concentrations were associated with reduced joint damage and this relationship was attenuated by adjustment for BMI, but enhanced by adjustment for inflammation. This finding suggests that the beneficial effects of leptin and BMI on radiographic damage may be related, and it may provide an explanation that contributes to understanding the observation that obesity is associated with less radiographic damage.

The mechanism whereby higher concentrations of leptin, generally considered to be pro-inflammatory, might reduce joint damage is not clear. However, leptin also has anabolic effects such as stimulating the expression of cartilage growth factors and increasing proteoglycan synthesis that could protect against joint damage(35). Animal studies have not clarified whether leptin is likely to promote or reduce joint damage; in different murine models of arthritis, leptin deficiency produced different responses, aggravating(36) or ameliorating(37) arthritis. Extrapolation of findings in leptin-deficient animal models to humans has been problematic(38). For example, leptin deficient mice are extremely obese, whereas obese humans have paradoxically high, rather than low, leptin concentrations. This is thought to reflect a state of leptin resistance in obese humans(39). If a similar condition of leptin resistance exists in other tissues, then higher leptin concentrations, which would

usually be expected to be pro-inflammatory, may not show these effects, and the reduced radiographic damage associated with obesity could be explained by such functional leptin deficiency. The observation that CRP directly inhibits the binding of leptin to its receptors and blocks its ability to signal *in vitro*(40) suggests that CRP may play a role in inducing leptin resistance. Thus, increased CRP concentrations could represent one mechanism responsible for inducing leptin resistance in RA. Indeed, concentrations of leptin and CRP were significantly correlated in our study.

Another explanation for the inverse association between leptin and radiographic damage is that high concentrations of leptin in RA do indeed act to promote joint damage, but these effects are overshadowed by another mediator also associated with obesity that protects against joint damage. A potential candidate would be adiponectin(1·3), an adipocytokine that has anti-inflammatory properties(5).

Adiponectin, like leptin, is strongly correlated with BMI, but unlike leptin the relationship is inverse, and its transcription is suppressed by inflammatory cytokines such as TNF- α and IL-6(4). Therefore, higher concentrations of adiponectin in patients with RA in our study are counterintuitive; however, this observation has also been made by others(15·16). Despite the higher concentrations of adiponectin in patients with RA, the inverse correlation with BMI remained. Thus, patients with higher BMI had lower concentrations of the anti-inflammatory adipocytokine, making it unlikely that adiponectin is related to the decreased radiographic joint damage in obesity. Indeed, adiponectin was weakly associated with higher and not lower Larsen scores.

Resistin, induces inflammatory cytokines and causes arthritis when injected into joints of mice(8). It is present in rheumatoid synovial tissue and fluid(15·41), and in a previous study was associated with higher Larsen scores despite not having higher serum concentrations in patients with RA than controls(42). We found that serum resistin concentrations were higher in RA, likely through inflammatory mechanisms, since after adjustment for inflammation statistical significance was lost. Resistin concentrations were weakly associated with Larsen score, and this was attenuated after adjustment for inflammation, suggesting similar mechanisms.

Limitations of the study include the cross sectional design and the unavailability of radiographs for the determination of Larsen score in some patients. However, apart from differences in age and BMI (variables that were adjusted for in all models) the demographic characteristics of patients with and without radiographs did not differ significantly. Larsen score could be affected by many variables but a sensitivity analysis that adjusted for a range of such variables, including the time between the date of enrollment and radiograph, yielded results that were essentially unchanged. Radiographs were not obtained at the same time that disease activity and adipocytokines were measured. Thus, the estimate of the relationship between adipocytokine concentrations and radiological damage may be less precise than would be the case if radiographs and blood samples had been obtained at the same time. Future longitudinal studies examining the relationship between visfatin concentrations and radiological damage, and studies to define the effects of inhibiting visfatin on arthritis in humans, as has been done in animal models(30), will provide important information.

In summary, concentrations of adipocytokines are increased in patients with RA and modulate radiographic joint damage. Visfatin is associated with RA, RF and increased radiographic damage. Leptin is associated with RA but with decreased radiographic damage.

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Figure 1. The Association between RA and Adipocytokines (n=167)

The association between RA and each individual adipocytokine was assessed using linear regression adjusted with a base model (age, sex and race), with BMI (base + BMI), inflammation (base + TNF- α , IL-6, and CRP), and both (base + BMI + inflammation). 10^b : Exponentiated linear regression coefficient of disease status (RA vs. controls). 10^b denotes the ratio of the mean adjusted serum adipocytokine concentrations of RA vs. controls. The translated percent difference with 95% CI is depicted on the figure.

Figure 2. The Association between Larsen Score and Adipocytokines (n=93)

OR: Odds ratio per IQR change of adipocytokine. The association of each individual adipocytokine with Larsen Score was assessed using proportional odds logistic regression adjusted with a base model (age, sex, race and disease duration), with BMI (base + BMI), inflammation (base + TNF- α , IL-6, and CRP), and both (base + BMI + inflammation).

Table 1

Clinical Characteristics and Adipocytokine Concentrations in Control and RA Groups

	Control (N=91)	RA (N=167)	P*
Age (years)	53.3±11.6	54.2±11.8	0.46
Sex (Males)	36.3%	31.1%	0.40
Race (Caucasian)	84.6%	88.6%	0.36
BMI (kg/m ²)	28.5±5.9	29.2±6.7	0.46
Current Smokers	8.8%	24.0%	0.003
Disease Duration (years)	-	3.0 [2.0–18.0]	-
RF Positive (%)	-	71.7%	-
DAS28	-	3.9 [2.7–4.9]	-
Larsen Score [†]	-	2.0 [0.0–16.0]	-
MHAQ Score	0.12±0.30	0.53±0.49	<0.001
CRP (mg/l)	0.6 [0.2–1.6]	4.0 [1.2–10.5]	<0.001
TNF- α (pg/ml)	3.4 [2.4–4.8]	5.5 [2.8–11.0]	<0.001
IL-6 (pg/ml)	4.3 [1.2–18.2]	13.8 [4.4–43.0]	<0.001
Leptin (ng/ml)	14.7 [5.2–29.5]	23.0 [9.5–38.9]	0.006
Resistin (ng/ml)	6.6 [4.9–8.5]	7.6 [5.6–11.4]	0.004
Adiponectin (ug/ml)	16.7 [9.5–31.1]	22.8 [14.8–38.7]	0.003
Visfatin (ng/ml)	3.8 [2.6–5.8]	6.0 [4.4–8.4]	<0.001

* P value obtained using Wilcoxon rank-sum or chi-squared tests.

Data are shown as mean±SD (standard deviation), median [IQR] (Interquartile Range) or percentages (%). BMI: Body Mass Index. MHAQ: Modified Health Assessment Questionnaire.

[†] n=93.

Table 2

Clinical Variables and Adipocytokines According to the Presence or Absence of Radiological Changes

	No Radiological Changes (N=44)	Radiological Changes (N=49)	P-value *
Age (Years)	53.3±10.5	58.5±11.6	0.03
Sex (Males)	34.1%	32.7%	0.88
Race (Caucasian)	93.2%	91.8%	0.81
BMI (kg/m ²)	28.3±5.8	26.8±5.0	0.29
Current Smokers	20.5%	22.4%	0.82
Disease Duration (Years)	2.4[1.6–5.3]	19.0[3.0–24.0]	<0.001
RF Positive (%)	67.4%	81.2%	0.13
DAS28	3.48[2.62–4.41]	3.98[2.79–4.92]	0.19
MHAQ Score	0.44 [0.0–0.75]	0.38 [0.0–1.13]	0.30
TNF- α (pg/ml)	4.7[2.5–7.8]	6.91[3.3–12.9]	0.12
IL-6 (pg/ml)	5.6[2.2–20.7]	18.6[7.7–55.3]	<0.001
CRP (mg/l)	3.0[1.0–7.3]	6.0[2.0–11.0]	0.09
Current Corticosteroid	75.0%	65.3%	0.31
Current Methotrexate	77.3%	69.4%	0.39
Current Leflunomide	13.6%	18.4%	0.54
Current TNF blocker	25.0%	22.4%	0.77
Leptin (ng/ml)	20.7[8.7–38.5]	20.8[5.6–29.7]	0.38
Resistin (ng/ml)	8.3[5.9–11.0]	9.0[5.7–13.6]	0.45
Adiponectin (ug/ml)	20.8[14.3–39.5]	26.5[18.6–38.8]	0.18
Visfatin (ng/ml)	5.7[4.7–7.2]	7.56[5.6–11.3]	0.002

Radiological change was defined as a Larsen score >0.

* P value obtained using Wilcoxon rank-sum or chi-squared tests.

Data are shown as mean±SD (standard deviation), median [IQR] (Interquartile Range) or percentages (%). BMI: Body Mass Index. MHAQ: Modified Health Assessment Questionnaire.

Table 3

Correlation (rho) between Adipocytokines and Clinical Variables in Patients with RA

Factor	Leptin	Resistin	Adiponectin	Visfatin
Age	-0.11	0.03	0.26**	0.02
BMI	0.58**	0.01	-0.39**	0.02
DAS28	0.23**	0.11	-0.09	0.13
Disease duration	0.01	0.03	0.19*	0.16*
Larsen Score	-0.10	0.07	0.19	0.38**
MHAQ Score	0.13	0.00	-0.08	0.18*
TNF- α	0.10	0.12	-0.01	0.23**
IL-6	0.17*	0.08	-0.01	0.42**
CRP	0.27**	0.15	-0.02	0.17*
Neutrophil count	0.06	0.27**	0.08	0.21**

Spearman Correlation Test.

*
p<0.05.**
p<0.01.