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Association of circulating adiponectin levels with progression of radiographic joint destruction in rheumatoid arthritis

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Abstract

Background—Adipokines have inflammatory and immunomodulatory properties that may contribute to erosive joint damage. The association of serum adipokine levels with progression of radiographic joint damage in patients with rheumatoid arthritis (RA) was prospectively explored.

Methods—Patients with RA underwent serum adipokine assessment (adiponectin, resistin, leptin) at three timepoints and hand/feet x-rays, scored using the Sharp-van der Heijde Score (SHS), at baseline and the third study visit, separated by an average of 39 ± 4 months. The associations of baseline and average adipokine levels with change in SHS were explored, adjusting for pertinent confounders.

Results—Of the 152 patients studied, 85 (56%) showed an increase in SHS (defined as >0 SHS units). Among the adipokines studied, only adiponectin was significantly associated with radiographic progression, with average adiponectin levels more strongly associated than baseline levels. After adjusting for average C reactive protein and baseline SHS, patients in the highest quartile of average adiponectin had a SHS progression rate more than double the lowest quartile (1.00 vs 0.48 units/year; $p=0.008$). Similarly, those in the highest quartile of adiponectin had a more than fivefold greater odds of any radiographic progression compared with the lowest quartile (OR 5.75; $p=0.002$). The magnitude of the association of average adiponectin levels with radiographic progression was greater in women, those with body mass index <30 kg/m² and those receiving baseline biological disease-modifying antirheumatic drugs.

Conclusions—These prospective data provide evidence of temporality and dose-response in the relationship between circulating adiponectin and erosive joint destruction in RA, and highlight subgroups of patients at highest risk for adiponectin-associated radiographic progression.

INTRODUCTION

Erosive joint destruction is a hallmark of rheumatoid arthritis (RA).¹ Accumulation of joint damage over time leads to progressive deformity and is a contributor to disability and reduced quality of life in patients with RA.² However, progression of erosive joint damage is variable among RA patients. Established risk factors for more rapid progression, such as

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RA-associated autoantibodies, genetic risk factors (ie, the HLA DRB1 'shared epitope') and chronically elevated synovial and systemic inflammation,³⁴ do not fully account for radiographic damage in most patients with RA, suggesting additional contributory mechanisms that remain to be elucidated.

The group of fat-derived hormones, collectively termed adipokines (eg, adiponectin, resistin, leptin and others) have recently been implicated in immune functioning, including proinflammatory properties in the joint.⁵⁶ Adiponectin, in particular, which shares sequence homology with tumour necrosis factor (TNF) α and complement C1q, has been cross-sectionally linked to erosive damage in RA⁷⁸ and erosive osteoarthritis.⁹ A mechanistic basis for these observations derives from in vitro and animal studies demonstrating the ability of adiponectin to activate proinflammatory pathways in synoviocytes,⁵⁶ leading to activation of proteases¹⁰¹¹ and osteoclasts¹² that may mediate damage to cartilage and bone. However, to date, only cross-sectional associations of adiponectin with radiographic damage have been reported. Longitudinal analyses are generally superior to those derived from cross-sectional data, since temporality is established and time-varying exposures and outcomes can be quantified.

We therefore sought to explore the associations of serum adipokine concentrations, at baseline and cumulative over follow-up, with change in radiographic damage scores in patients with RA enrolled in a prospective cohort study. We hypothesised that higher serum adipokine levels—particularly adiponectin—would be associated with radiographic progression in patients with RA, even after controlling for pertinent confounders.

METHODS

Study participants and timing of visits

Study subjects were participants in the Evaluation of Subclinical Cardiovascular disease And Predictors of Events in Rheumatoid Arthritis (ESCAPE RA), a cohort study investigating the prevalence, progression and risk factors for subclinical cardiovascular disease in RA. A total of 197 patients with RA completed the baseline study visit, all of whom met the 1987 classification criteria for RA,¹³ were 45–84 years of age and did not report any prior pre-specified cardiovascular events or procedures. The study was approved by the Institutional Review Board of the Johns Hopkins Hospital. Enrolment began in October 2004 and concluded in May 2006. A total of 186 (94%) returned for the second visit, which occurred an average of 21 ± 3 months after baseline, and 158 (80%) returned for the third study visit which occurred an average of 39 ± 4 months after baseline.

Assessments

Radiographic outcomes—Single-view anterior-posterior x-rays of the hands and postero-anterior x-rays of the feet were obtained at the first and third visits and scored using the van der Heijde modification of the Sharp method (SHS)¹⁴ by a single experienced reader blinded to patient characteristics and aware of image sequence. Among the 158 participants completing the study, 152 had evaluable x-rays from both timepoints. Seven participants had incomplete radiographic assessments (three were missing a single hand film, two were missing a single foot film and two had complete hand x-rays but were missing both foot films). For those missing a single film, the missing score (hand or foot) was imputed from the available hand or foot. For the two participants missing both foot films, an imputed score was derived from the cohort based on the expected foot scores given the available hand scores. Primary analyses utilised imputed scores, with sensitivity analyses including only participants with extant films.

Body composition assessments—Subjects underwent total body dual-emission x-ray absorptiometry (DXA) scanning on a Lunar Prodigy DXA scanner (GE/Lunar Radiation, Madison, Wisconsin, USA) to measure total and regional fat and lean mass. Body mass index (BMI) was calculated as body weight (kg)/height (m²).

Sociodemographic, lifestyle and RA covariates—Age, gender, race/ethnicity and current and past smoking were assessed by patient self-report. Forty-four joints were examined for swelling and tenderness by a single trained assessor and RA disease activity calculated using the Disease Activity Score for 28 joints with C reactive protein (CRP) (DAS28-CRP).¹⁵ The Stanford Health Assessment Questionnaire¹⁶ was used to assess disability. Current and past use of glucocorticoids, biological and non-biological disease-modifying antirheumatic drugs (DMARDs) was determined by detailed examiner-administered questionnaires.

Laboratory assessments—Fasting blood samples were collected at each study visit (total three repeated measures per participant). Adipokines (total adiponectin, resistin, leptin) were measured by ELISA at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont, USA). CRP was measured by nephelometry (Dade Behring, Deerfield, Illinois, USA). Rheumatoid factor was assessed by ELISA, with seropositivity defined at or above a level of 40 units. Anti-CCP antibody was assessed by ELISA, with seropositivity defined at or above a level of 60 units. PAD4 antibodies were measured by immuno-precipitation as previously described.¹⁷ Exon 2 of HLA-DR1 was sequenced for shared epitope alleles as previously described.¹⁸

Statistical analysis

The distributions of all variables were examined. Cumulative averages of repeated measures of continuous variables (ie, adipokine concentrations, inflammatory markers) were calculated from the area under the curve divided by the total number of days between repeated measures. Univariate robust regression models were constructed to explore total SHS progression rate (units/year) with participant characteristics included as covariates, with β coefficients, 95% CIs and their associated p values calculated. Robust regression was used to reduce the potential influence of leveraging outliers. Multivariable models were constructed first in extended models including all covariates with associations from univariate models $p < 0.20$ (to allow for residual confounding). Simpler models were then constructed by excluding the covariates with the weakest associations with the outcome, with the impact of excluding the covariate tested using Akaike's Information Criterion for nested models. Variance inflation factors were calculated to ensure that variables with excessive collinearity were not modelled simultaneously (ie, RA duration and baseline SHS). We sought to isolate the independent associations of baseline and average adipokine levels with radiographic progression; selection of confounders was therefore restricted to covariates associated with both the outcome and exposure, without being a potential intermediate.

Multivariable ordinary logistic regression was used to model radiographic progression as a dichotomous variable using a modelling strategy similar to that described for robust regression, with the exception of the likelihood ratio test used for testing nested models. Any change in SHS (ie, yearly average rate of change >0 SHS units) was the primary dichotomous outcome used; however, sensitivity analyses were conducted with the alternative outcome of any increase in SHS of ≥ 4 units. Potential heterogeneities in the associations of covariates with change in SHS across strata of characteristics were modelled in interaction models and tested using analysis of covariance. All statistical calculations

were performed using Intercooled Stata 10 (StataCorp, College Station, Texas, USA). A two-tailed α of 0.05 was used throughout.

RESULTS

The characteristics of the 152 patients with RA are summarised in table 1. The median baseline SHS was 8 units and increased by a median of 0.31 units per year. Any increase in SHS was observed in 85 patients (56%), with 29% of the total group having 4 units of progression. Among those with progression, the median yearly change in SHS was 1.5 units.

Univariate associations of patient characteristics with change in SHS

Univariate associations of patient characteristics with the average yearly change in total SHS and the probability of any progression of SHS are summarised in table 2. Characteristics significantly associated with SHS change included current smoking, longer RA duration, any HLA DRB1 'shared epitope' alleles, higher baseline SHS and serum adiponectin concentration. While both baseline and average adiponectin levels were significantly associated with change in SHS, the magnitude of the change in SHS was greater for average adiponectin levels (average yearly increase in SHS=0.34 units per log increase in average adiponectin; $p=0.010$) than for baseline adiponectin levels (average yearly increase in SHS=0.26 units per log increase in baseline adiponectin; $p=0.014$). Neither baseline nor average levels of other adipokines (resistin, leptin) were associated with change in SHS in univariate analyses. Similar associations were demonstrated when any SHS progression was modelled as the outcome.

Univariate associations of patient characteristics with average adiponectin concentration

Univariate associations of patient characteristics with the log of the average serum adiponectin concentration are summarised in table 3. Higher baseline age was associated with higher average adiponectin levels. Men, non-Caucasians and ever smokers had significantly lower average adiponectin levels than women, Caucasians and never smokers, respectively. As expected, higher baseline BMI was associated with lower average adiponectin levels and, among measures of body fat, truncal fat was the measure with the strongest inverse association with adiponectin. Patients with higher baseline SHS and those prescribed prednisone at baseline had significantly higher average adiponectin levels. Other treatment characteristics were not significantly associated with average adiponectin levels in univariate analyses.

Adjusted associations of average serum adiponectin concentration with change in SHS

Specifics of multivariable model building, constructed with the goal of isolating the independent associations of quartiles of serum adiponectin levels with measures of change in SHS are summarised in table S1 (modelling the continuous outcome of average yearly change in SHS) and table S2 in the online supplement (modelling the categorical outcome of any increase in SHS). For both outcomes, average CRP and baseline SHS were the only confounders retained in the final models, in addition to the independent covariate of interest (average adiponectin concentration, categorised into quartiles in order to explore nonlinear associations with the outcomes).

Crude and adjusted associations of quartiles of average serum adiponectin concentration that derive from these models are graphically depicted in figure 1. Before adjustment (figure 1A), those in the fourth quartile of average adiponectin had an average yearly increase in SHS that was 0.44 units higher than those in the first quartile (0.65 vs 0.21 units/year, respectively, a threefold higher rate; $p=0.014$). After adjustment for average CRP and baseline SHS, the difference in SHS between outer quartiles of average adiponectin was

increased to 0.53 units (1.00 vs 0.48 units, a twofold higher rate; $p=0.008$). In adjusted analysis, the association of quartiles of average adiponectin with SHS progression rate was not linear, as the association was similar among the first three quartiles and increased meaningfully over baseline only for those in the fourth quartile. For the categorical outcome of any increase in SHS, before adjustment (figure 1B) 68% of those in the fourth quartile of average adiponectin showed radiographic progression compared with 38% of those in the first quartile (OR 3.57; $p=0.009$). After adjustment, 77% of those in the fourth quartile of average adiponectin showed radiographic progression compared with 37% of those in the first quartile (OR 5.75; $p=0.002$). In adjusted analyses the association of quartiles of average adiponectin levels with the frequency of radiographic progression was linear. In analyses excluding participants with imputed SHS, the magnitude of the association of adiponectin with SHS progression was not meaningfully altered, and statistical significance was retained (data not shown). In an additional sensitivity analysis we modelled the association of quartiles of average adiponectin levels with the categorical outcome of an increase in SHS of 4 units (figure S1 in online supplement). This association was similar to that observed with the other outcomes.

Comparison of the associations of average adiponectin levels with radiographic progression among subgroups of RA patients

Heterogeneities in the association of average serum adiponectin concentration with the adjusted probability of any radiographic progression according to subgroups of patients with RA are summarised in table 4. Three dichotomous characteristics (gender, BMI ≥ 30 kg/m² and baseline use of biological DMARDs) demonstrated significant differences in the associations of average adiponectin levels with radiographic progression depending on stratum, while two additional characteristics (anticitrullinated peptide antibody seropositivity and baseline prednisone use) had p values for interaction that were >0.05 but <0.10 . Differences in associations for the significant characteristics are graphically depicted in figure 2. In analyses stratified by gender (figure 2A), the average adiponectin level was strongly associated with the adjusted probability of radiographic progression in women (OR 5.94 per log unit; $p=0.004$) but was not associated in men (OR 0.75 per log unit; $p=0.59$). Low average adiponectin levels were associated with a lower probability of radiographic progression than higher levels in the subgroup of patients with a BMI <30 kg/m² (figure 2B). In contrast, for those with a BMI ≥ 30 kg/m², lower levels of adiponectin were associated with a statistically similar adjusted probability of radiographic progression as higher levels, which was also similar to the group with BMI <30 kg/m² with the highest adiponectin levels. For patients with RA prescribed biological agents at baseline (figure 2C), lower average adiponectin levels were associated with a lower adjusted probability of radiographic progression compared with those with higher levels (OR 15 per log unit; $p=0.003$), an association that was not as pronounced in those not prescribed biological agents (OR 1.5 per log unit; $p=0.35$). Patients prescribed biological agents with low adiponectin levels had a lower adjusted probability of radiographic progression than patients not prescribed biological agents with similar average adiponectin levels. In contrast, patients with high average adiponectin levels who were receiving biological agents at baseline had a higher adjusted probability of radiographic progression than those not receiving biological agents with similar average adiponectin levels.

DISCUSSION

In this investigation, the first to our knowledge to report longitudinal associations of serum adipokine levels with progression of radiographic damage in RA, we observed a higher average yearly rate of SHS progression in patients with RA with higher average serum adiponectin levels than in those with lower levels, and a more than fivefold greater odds of

radiographic progression among those in the highest quartile of average adiponectin levels compared with the lowest quartile. These associations remained significant even after adjusting for pertinent confounders. Furthermore, the magnitude of the association of average adiponectin levels with radiographic progression was greater in women than in men, in those with BMI <30 kg/m² than in those with higher BMI levels, and in those receiving biological DMARDs at baseline compared with those not treated with biological DMARDs. We did not observe any meaningful associations of baseline or average levels of other adipokines (resistin or leptin) with radiographic progression.

These findings are consistent with recent human in vitro studies linking adiponectin to synovial inflammation. Adiponectin has been shown to increase the expression of interleukin 6 in cultured synovial fibroblasts of patients with RA and osteoarthritis.⁵⁶ Other identified functions of adiponectin that potentially contribute to joint destruction include stimulation of osteoclast differentiation via increasing RANKL and decreasing osteoprotegerin,¹² upregulation of vascular endothelial growth factor and matrix metalloproteinases¹⁰ and increased production of chemokines and chemokine receptors¹¹ in synoviocytes, chondrocytes, lymphocytes and endothelial cells. Taken together, these studies suggest a central role for adiponectin across the spectrum of processes that lead to erosive joint destruction in RA.

There is evidence for other adipokines as contributors to synovial inflammation. In particular, resistin stimulated the production of inflammatory cytokines in macrophages¹⁹ and, when injected into mice, produced an RA-like inflammatory destructive polyarthropathy.²⁰ However, none of the human cross-sectional investigations have demonstrated a strong signal for the contribution of resistin to erosive damage.^{8,21} Likewise, our prospective data provide no confirmation. These findings could indicate that resistin plays less of a role in synovial inflammation in human RA than that suggested from animal studies, or that circulating levels might not correlate with relevant synovial levels. In support of this, resistin levels in synovial fluid have been shown to be higher than circulating levels.²⁰

We identified some interesting subgroup differences in the association of serum adiponectin with radiographic progression. First, higher average levels of adiponectin were only associated with radiographic progression in women. The mechanisms behind this heterogeneity are not readily apparent as they were not explained by gender differences in demographics, lifestyle factors or RA disease activity or severity measures. Hormonal effects on adiponectin signaling and/or susceptibility of bone to damage are possible mediating mechanisms that warrant additional investigation. In addition, lower adiponectin levels were not associated with a lower probability of radiographic progression in obese patients with RA, suggesting that adiposity-associated factors, other than those studied, contribute to joint damage. The combination of low adiponectin levels and biological DMARD use was associated with a low probability of radiographic progression. However, the protective effect of biological DMARDs was lost in patients with the highest average adiponectin levels, suggesting an antagonistic interaction that may be useful in identifying patients at risk of radiographic progression despite aggressive therapy. Since almost all of the patients receiving baseline biological agents were prescribed TNF inhibitors, it is unclear whether these effects would be observed with other biological agents. Although interesting, these subgroup analyses must be interpreted with care as the smaller sample sizes of the subgroups increase the uncertainty of the estimates and should be considered hypothesis-generating. However, given the conservative nature of significance testing for interaction, the differences in association observed for gender, obesity and use of biological agents are sufficiently robust to warrant additional investigation into the mechanism.

There are some further notable limitations to our study. Owing to oligomerisation,²² adiponectin exists in a number of isoforms which may have differential effects on radiographic progression that were not captured with our total adiponectin assay. In addition, circulating levels may not be the same as those at the level of the joint. However, neither of these limitations impugns the observed associations between circulating adiponectin and radiographic progression. Also, we calculated cumulative average levels for adipokines from repeated measures from three timepoints spanning more than 3 years, a method that may have missed relevant changes in levels between visits. However, our observation that average levels were more strongly associated with radiographic outcomes than baseline levels suggests that our averaging method was superior to simply using the baseline level as our primary exposure variable of interest. Finally, medication use was not randomly allocated, so confounding by indication must be considered when interpreting any beneficial or detrimental effects of treatments.

In summary, our prospective findings of greater radiographic progression among patients with RA with higher average adiponectin levels provides additional human corroboration of in vitro studies suggesting a mechanistic link between adiponectin and erosive joint damage. In addition, the effect of adiponectin on joint destruction may differ between subgroups of patients with RA defined by gender, obesity and pharmacotherapies. Extending these findings, selective targeting of the effects of adiponectin on the joint may be a strategy for preventing erosive joint damage in individuals with RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Crude and adjusted associations of quartiles of average serum adiponectin levels with (A) the average yearly change in Sharp-van der Heijde score and (B) the proportion of participants with radiographic progression (ie, an increase in Sharp-van der Heijde score >0). Analyses were adjusted for average C reactive protein and baseline Sharp-van der Heijde scores. Means and 95% CIs are depicted. Quartiles of adiponectin concentration: Q1=4.8–20.8 mg/l; Q2=20.9–32.1 mg/l; Q3=32.2–43.3 mg/l; Q4=43.3–79.6 mg/l.

Figure 2.

Adjusted average probability of any radiographic progression (ie, an increase in Sharp-van der Heijde score >0) according to the log average serum adiponectin level in patients with rheumatoid arthritis subdivided by (A) gender, (B) body mass index (BMI) above and below 30 kg/m^2 and (C) the use of biological disease-modifying antirheumatic drugs (DMARDs) at baseline. Upper and lower 95% confidence limits are depicted by the thin grey line surrounding the average probability function. In each panel the p value for interaction testing the difference in the associations of adiponectin with the probability of radiographic progression was <0.05 .

Table 1

Patient characteristics

	Total patients (n=152)
Age, years	59 ± 8
Male, n (%)	57 (38)
Caucasian, n (%)	133 (88)
Ever smoking, n (%)	86 (57)
Current smoking, n (%)	15 (10)
BMI, kg/m ²	28.1 ± 5.0
BMI <25, n (%)	43 (28)
25 ≤ BMI <30, n (%)	58 (38)
BMI ≥ 30, n (%)	51 (34)
Total fat, kg	29.5 ± 10.2
Truncal fat, kg	16.0 ± 6.0
Appendicular fat, kg	13.4 ± 5.1
RA duration, years	9 (4–17)
RF seropositive, n (%)	91 (60)
ACPA seropositive, n (%)	101 (67)
Any shared epitope alleles, n (%)	107 (71)
Anti-PAD4 antibody seropositive, n (%)	23 (15)
DAS28, units	3.6 (2.9–4.3)
HAQ, units	0.69 (0.13–1.25)
Baseline CRP, mg/l	2.2 (1.1–6.4); range (0.2–101.0)
Average CRP, mg/l	3.1 (1.3–6.5); range (0.2–54.4)
IL-6, ng/ml	3.6 (1.7–7.5); range (0.4–107)
Average IL-6, ng/ml	4.4 (2.8–11.5); range (0.8–131)
Baseline non-biological DMARD use, n (%)	131 (86)
Baseline biological DMARD use, n (%)	67 (44)
Continuous use during study, n (%)	52 (34)
Discontinued use during study, n (%)	13 (9)
Initiated use during study, n (%)	
Baseline prednisone, n (%)	54 (36)
Cumulative oral prednisone, g *	4.1 (1.2–6.1); range (0.01–14.0)
Any intra-articular injections, n (%)	28 (18)
Baseline total SHS	8 (0–41)
Baseline erosion score	3 (0–16)
Baseline JSN score	5 (0–24)
SHS change, units/year	0.31 (0–1.64)
Any increase in SHS >0 units, n (%)	85 (56)
Any increase in SHS ≥ 4 units, n (%)	44 (29)
SHS change (progressors only), units/year	1.49 (0.62–3.51)
Adiponectin, mg/l	

	Total patients (n=152)
Baseline	32 (20–43)
Cumulative average	32 (21–43)
Resistin, ng/ml	
Baseline	16 (12–20)
Cumulative average	17 (14–22)
Leptin, ng/ml	
Baseline	14 (7– 27)
Cumulative average	15 (9–30)

Results are mean $\pm$ SD or median (IQR) unless otherwise noted.

* Among the 72 participants who received any oral prednisone during the study interval.

ACPA, anticitrullinated peptide antibodies; BMI, body mass index; DAS, Disease Activity Score; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; JSN, joint space narrowing; IL, interleukin; PAD, peptidyl arginine deiminase; RA, rheumatoid arthritis; RF, rheumatoid factor; SHS, Sharp-van der Heijde score.

Table 2

Association of patient characteristics with measures of change in Sharp-van der Heijde scores

	Average yearly		Any SHS progression	
	Δ Total SHS			
	β^*	p Value	OR [†]	p Value
Age, per year	0.007	0.34	1.04	0.082
Male vs female	-0.183	0.095	0.47	0.026
Caucasian vs other	-0.194	0.23	0.54	0.23
Ever smoking vs never	0.166	0.21	1.02	0.94
Current smoking vs non-smoking	0.373	0.034	1.22	0.72
BMI, per kg/m ²	0.002	0.87	1.00	0.88
Total fat, per kg	0.0001	0.99	1.01	0.74
Truncal fat, per kg	-0.010	0.34	0.97	0.33
Appendicular fat, per kg	0.018	0.15	1.06	0.069
RA duration, per year	0.020	0.001	1.05	0.008
RF seropositive vs negative	0.075	0.53	1.23	0.53
ACPA seropositive vs negative	0.054	0.65	1.12	0.74
Any shared epitope alleles vs none	0.250	0.044	2.24	0.028
Anti-PAD4 antibody seropositive vs negative	0.025	0.87	1.99	0.16
DAS28, per unit	0.005	0.92	1.37	0.053
Log average CRP, per log mg/l	0.085	0.093	1.62	0.001
Log average IL-6, per log ng/ml	0.098	0.079	1.71	0.001
Log baseline SHS, per log unit	0.277	<0.001	2.01	<0.001
Baseline non-biological DMARD use vs non-use	-0.002	0.99	1.16	0.75
Baseline biological DMARD use vs non-use	-0.113	0.36	0.92	0.80
No biological agents used over study	Referent	–	Referent	–
Discontinued biological agents during study	-0.354	0.13	0.53	0.30
Initiated biological agents during study	-0.082	0.69	2.02	0.23
Continuous biological agent use	-0.072	0.61	1.15	0.71
Baseline prednisone use vs non-use	0.027	0.82	1.05	0.88
Cumulative oral prednisone, per g	0.005	0.75	0.99	0.98
Any intra-articular injections vs none	0.123	0.38	1.89	0.15
Log baseline adiponectin, per mg/l	0.255	0.014	2.34	0.003
Log average adiponectin, per mg/l	0.339	0.010	2.53	0.004
Log baseline resistin, per ng/ml	0.195	0.23	1.14	0.74
Log average resistin, per ng/ml	0.146	0.41	0.86	0.74
Log baseline leptin, per ng/ml	-0.011	0.84	0.99	0.96
Log average leptin, per ng/ml	0.010	0.86	1.05	0.77

* β Coefficients represent the average change in SHS (units/year) occurring with an increase of 1 unit in the independent variable of interest. For dichotomous variables a change of 1 unit represents the difference between those with and those without the variable.

† ORs represent the average ratio of odds of any SHS progression for patients with the independent variable of interest compared with the same patients with an increase of 1 unit in the variable.

ACPA, anticitrullinated peptide antibodies; BMI, body mass index; CRP, C reactive protein; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IL, interleukin; JSN, joint space narrowing; PAD, peptidyl arginine deiminase; RA, rheumatoid arthritis; RF, rheumatoid factor; SHS, Sharp-van der Heijde score.

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Table 3

Univariate associations of patient characteristics with the log average serum adiponectin level

	β^*	p Value
Age, per year	0.012	0.024
Male vs female	-0.438	<0.001
Caucasian vs other	0.339	0.011
Ever smoking vs never	-0.245	0.006
Current smoking vs non-smoking	-0.167	0.28
BMI, per kg/m ²	-0.023	0.007
Total fat, per kg	-0.005	0.29
Truncal fat, per kg	-0.021	0.003
Appendicular fat, per kg	0.012	0.17
RA duration, per year	0.008	0.074
RF seropositive vs negative	-0.080	0.38
ACPA seropositive vs negative	-0.038	0.70
Any shared epitope alleles vs none	0.147	0.13
Anti-PAD4 antibody seropositive vs negative	0.113	0.37
DAS28, per unit	0.027	0.53
Log average CRP, per log mg/l	-0.048	0.19
Log average IL-6, per log ng/ml	0.047	0.24
Log baseline SHS score, per log unit	0.072	0.042
Baseline non-biological DMARD use vs non-use	-0.098	0.45
Baseline biological DMARD use vs non-use	0.092	0.31
No biological agents used over study	Referent	–
Discontinued biological agents during study	-0.007	0.97
Initiated biological agents during study	0.237	0.11
Continuous biological agent use	0.148	0.14
Baseline prednisone use vs non-use	0.183	0.045
Cumulative oral prednisone, per g	0.016	0.25
Any intra-articular injections vs none	0.049	0.67

* β Coefficients represent the average change in log average serum adiponectin level occurring with an increase of 1 unit in the independent variable of interest. For dichotomous variables a change of 1 unit represents the difference between those with and those without the variable.

ACPA, anticitrullinated peptide antibodies; BMI, body mass index; CRP, C reactive protein; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; IL, interleukin; PAD, peptidyl arginine deiminase; RA, rheumatoid arthritis; RF, rheumatoid factor; SHS, Sharp-van der Heijde score.

Table 4

Effect modification of the adjusted association of log average adiponectin levels with the odds of progression of Sharp-van der Heijde scores according to stratum of patient characteristics

	Association of log average adiponectin with the odds of radiographic progression in patients without the indicated characteristic		Association of log average adiponectin with the odds of radiographic progression in patients with the indicated characteristic		p Value for interaction [†]
	OR*	p Value	OR*	p Value	
Age > median	2.06	0.12	3.25	0.063	0.55
Male	5.94	0.004	0.75	0.59	0.010
Caucasian	1.39	0.69	3.66	0.005	0.30
BMI <25 kg/m ²	2.78	0.024	1.68	0.49	0.56
BMI >30 kg/m ²	4.69	0.002	0.83	0.78	0.037
Total fat > median	2.22	0.11	2.99	0.053	0.69
Truncal fat > median	4.60	0.010	1.27	0.65	0.10
RA duration < median	1.88	0.18	3.41	0.039	0.43
RF seropositive	1.73	0.28	3.43	0.020	0.34
ACPA seropositive	1.19	0.78	4.25	0.003	0.098
Any shared epitope	1.45	0.54	3.37	0.011	0.27
DAS28 > median	4.35	0.013	1.61	0.33	0.19
Baseline biological agents	1.50	0.35	15.03	0.003	0.020
Baseline prednisone use	4.19	0.004	1.12	0.85	0.089

* ORs represent the average ratio of odds of any SHS progression for patients with the independent variable of interest compared with the same patients with an increase of 1 unit in the variable. For dichotomous variables a change of 1 unit represents the difference between those with and those without the variable.

[†] p Value for interaction is for the test of heterogeneity of the association of log average adiponectin with the odds of radiographic progression between those with and those without the independent variable of interest.

ACPA, anticitrullinated peptide antibodies; BMI, body mass index; DAS, disease activity score; RA, rheumatoid factor; RF, rheumatoid factor.