Associations between body mass, radiographic joint damage, adipokines and risk factors for bone loss in rheumatoid arthritis

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Abstract

Objective. To evaluate the association between BMI and radiographic joint damage (RJD) in RA.

Methods. van der Heijde-Sharp (vdHS) erosion scores were determined in 499 participants with RA, ages 18–85 years, while enrolled in a clinical trial of golimumab (GO-BEFORE trial). Subjects were MTX and biologic therapy naïve. Multivariable logistic regressions determined the odds of prevalent RJD (defined as vdHS score >10) according to BMI category. Longitudinal analyses evaluated the association between BMI category and progression of vdHS score over 52 weeks. Analyses in a subset of 100 participants examined the association between adipokines and vdHS scores.

Results. At enrolment and 52 weeks, 37.6 and 43.6% of participants had RJD. Compared with normal weight, obese subjects had lower odds of RJD [0.40 (95% CI 0.22, 0.74); P = 0.003], and underweight subjects had greater odds [3.86 (95% CI 1.66, 9.00); P = 0.002] at baseline, adjusted for demographic and disease characteristics. The baseline associations between BMI category and RJD were greater among participants with multiple risk factors for bone loss (female >50 years, smoking, glucocorticoid exposure and vitamin D deficiency); test for interaction P = 0.05. Adjustment for adiponectin levels did not attenuate the association between BMI and vdHS scores. Baseline BMI and change in weight did not independently predict radiographic progression (P > 0.1).

Conclusions. Higher BMI was independently associated with less RJD and was greatest in participants with risk factors for bone loss. Future studies are needed to examine the associations between RJD, obesity, weight loss and osteoporosis.

Key words: Rheumatoid arthritis, Body mass index, Erosion, Disease activity, Adipokines, Adiponectin.

Introduction

RA is an inflammatory disease characterized by joint destruction and deformity [1]. Joint destruction is variable, and research has focused on identifying predictors of progression of joint damage. Historically, BMI has been included in RA research as a potential confounder, but has been largely ignored as a possible contributor to disease. Recently, several studies have suggested that a greater BMI may be associated with less radiographic joint damage (RJD) [2–6].

Prior studies of the effect of BMI on progression of RJD yielded conflicting results. A small study of 54 subjects identified an association between lower BMI and progression of RJD in early RA [2]. Several larger studies have since confirmed these results, but found that the association was only present in seropositive subjects [3–5]. A study of subjects with longer disease duration did not confirm this association and instead found that both high and low BMIs were associated with worse function and...
disease activity, but not with erosion scores [7]. Differences in study outcomes may be the result of variation in study size, heterogeneity of study subjects or incomplete controlling for potential confounders.

The mechanism for the association between BMI and RJD has not been established. Lower BMI could be the consequence of more severe disease, although associations have been independent of traditional measures of disease severity. Alternatively, adipose tissue produces inflammatory cytokines known as adipokines [8]. Several adipokines have been studied with regard to the association between BMI and RJD in RA, but the results have been inconclusive. Greater weight is protective against age-related bone loss; therefore, bone health may represent another possible link between greater BMI and less severe RJD that has not been studied. Greater bone density at the femoral head has been shown to correlate with less progression of erosive disease [9]. Mechanical loading imposed by increased weight may have a positive influence on bone homeostasis and may prevent joint destruction in other settings, as has been suggested in OA [10].

This ancillary study was conducted within a random sample of 499 participants in the Trial of Efficacy and Safety of Golimumab Treatment of Rheumatoid Arthritis of Early Onset (GO-BEFORE) clinical trial. The objectives were to evaluate the association between baseline BMI and concurrent RJD and the association between BMI and the progression of RJD over 52 weeks in a large cohort of subjects with active RA and standardized assessment of RJD. Secondary objectives were to determine the associations between BMI and disability scores and to determine if the association between BMI and RJD differed according to the presence of risk factors for bone loss. In addition, we explored the association of BMI, adipokines and joint damage in a subset of 100 participants.

Methods

Study setting

This study is a secondary analysis of the GO-BEFORE trial (Clntrials.gov identifier NCT00361335), a multicentre, double-blind, placebo-controlled trial that compared the efficacy of MTX or golimumab, a fully human mAb with TNF-α, to combination therapy with both agents for the treatment of RA. A total of 637 RA patients were enrolled and followed for 52 weeks between 2005 and 2007. The trial results have been previously published [11].

The trial recruited patients aged ≥ 18 years from sites in Asia, Europe, Australia, Latin America and North America. Subjects met ACR criteria for a diagnosis of RA and were MTX and biologic therapy naive. Subjects had active disease, defined by having at least four swollen and four tender joints and at least two of the following: (i) an elevated ESR (>28 mm/h) or CRP (>1.5 mg/dl), (ii) erosions on radiographs, (iii) an elevated cyclic citrullinated peptide (CCP) antibody titre or RF or (iv) the presence of morning stiffness >30 min. Informed consent was obtained in the original study.

This ancillary study was conducted in a random sample of 499 subjects (80% sample) selected by a random number generator and evaluated for the risk of erosive disease based on BMI category. This study was approved by the Internal Review Board at the University of Pennsylvania.

Data collection

Patient’s visits occurred at 4-week intervals and included independent, blinded assessments of 28-joint DASs incorporating CRP (DAS-28(CRP)). Subjective assessment of overall patient disability was measured with the HAQ score. Based on previous definitions, abnormal HAQ was defined as a HAQ > 1 [12]. Whole blood samples were sent to Quintiles Central Laboratories for all standard laboratory studies as part of the original trial. Estimated glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease (MDRD) study equation [13]. Adipokine levels (adiponectin and leptin) were measured on baseline samples of 100 subjects by Rules-Based Medicine (Austin, TX, USA) as part of an 88-biomarker multi-analyte profile. 25(OH) vitamin D levels were performed on stored serum at Heartland Assays (Ames, IA, USA). Vitamin D deficiency was defined as <20 ng/ml. Other non-laboratory variables evaluated include patient-reported regular aerobic exercise (yes/no), a history of smoking (ever/never) and patient-reported history of diabetes mellitus, hypertension and glucocorticoid therapy at baseline.

As part of the trial, plain radiographs of the hands and feet were performed at baseline and Week 52 using standard methods. Radiographs were assessed as previously described using the average scores of two, blinded, centralized readers [14]. The two components of the van der Heijde–Sharp (vdHS) score—erosion score and joint-space narrowing score—were also analysed separately. The vdHS scores were highly skewed. Based on the appearance of the histogram, an a priori cut-off score of 10 was concluded as optimal in this group in separating normal variation from true RA-related RJD. Subjects with a vdHS score > 10 were considered to have RJD.

Statistical analysis

Data were analysed with STATA 11 software (StataCorp, LP, College Station, TX, USA). Patients were divided into categories according to BMI (kg/m²). Underweight was defined as a BMI <20 kg/m², normal weight (20–24.9 kg/m²), overweight (25–29.9 kg/m²) and obese (≥ 30 kg/m²). When treated as a binary exposure variable, a cut-off of 25 kg/m² was used to define elevated BMI. Subject characteristics were described for each BMI category. Associations between BMI category and continuous variables were assessed using analysis of variance (ANOVA) and Kruskal–Wallis tests of significance. Spearman’s correlations were used to evaluate associations between continuous variables. Variables identified as potential confounders of RJD by BMI category were included in the regression models.
Baseline characteristics were used to inform a multivariable logistic regression model, assessing the risk of having an elevated vdHS score. Normal weight was used as the reference group. This was performed separately for the two components of vdHS score—erosion and joint-space narrowing. Logistic regression was preferred over linear regression since the vdHS scores were highly skewed. When vdHS scores were used as the outcome in linear regression in a subsample, they were log-adjusted to fit a normal distribution. Final multivariable models included age, sex, race, smoking history, albumin, GFR, ESR at baseline, CCP status, CS use at baseline, disease duration and disease activity at baseline as measured by DAS-28(CRP).

Other variables initially assessed in the model included serum 25(OH) vitamin D level, HAQ score, regular exercise, geographic region, RF status, pain scores and subsequent loss of weight over the first 24 weeks.

In order to assess the association between BMI and disability, the odds ratio (OR) of having an abnormal HAQ score was also assessed by BMI category controlling for age, sex, race, smoking history, albumin, GFR, ESR at baseline, CCP status, CS use at baseline, disease duration and baseline DAS-28(CRP). Since the previous studies did not find consistent associations between BMI and joint destruction within all subgroups, we evaluated for effect modification in specific subgroups of hypothetical interest, including subjects with and without risk factors for bone loss. Previously established risk factors for osteoporosis that were available included age, sex, BMI, race, glucocorticoid use, smoking history and vitamin D levels [15]. These factors were evaluated as effect modifiers of the BMI effect on RJD. This was performed for each risk factor and then with an ordinal indicator variable for the number of risk factors.

Multivariable linear regression was performed on a subset of 100 subjects with adipokine levels. The independent associations between a log-transformed vdHS score and adipokine levels, leptin levels and BMI were assessed controlling for potential confounders.

A change of vdHS score from baseline at 52 weeks of >0.5 was considered progression (as it was in the original trial). This cut-off ensures agreement among radiologists that radiographic progression has occurred for each individual subject. Chi-squared testing was used to assess for significant differences in progression between BMI categories. Multivariable logistic regression was performed to evaluate the risk of radiographic progression for each category of BMI controlling for age, race, sex, DAS-28(CRP), CCP status, GFR, albumin, smoking, CS use, ESR, disease duration, treatment group and baseline vdHS scores. Similar models evaluated the association between changes in BMI and radiographic progression. We also evaluated for effect modification by treatment group.

Results

Baseline characteristics

Characteristics of subjects at the time of enrolment by BMI category are shown in Table 1. Of the 499 subjects studied, 8.2% were underweight (BMI < 20 kg/m²), 31.2% were normal weight (BMI 20–24.9 kg/m²), 35.1% were overweight (BMI 25–29.9 kg/m²) and 25.5% were obese (BMI ≥ 30 kg/m²). Overweight and obese patients were older, more likely to be Caucasian, more likely to be seronegative and more likely to smoke. Underweight patients had a lower albumin, higher GFR and higher ESR and CRP concentrations. Pain score was higher and vitamin D levels were lower in overweight and obese patients, but there was no significant difference in baseline tender or swollen joint count, HAQ, disease duration or DAS across BMI categories.

BMI and radiographic damage

vdHS score, erosion score and joint-space narrowing scores were significantly different across BMI categories, with lower median scores in higher BMI categories. The distribution of vdHS scores by BMI category is shown in Fig. 1. There was a negative correlation between BMI and total vdHS score (Spearman’s ρ = −0.18, P = 0.0001), erosion score (Spearman’s ρ = −0.14, P < 0.01) and joint-space narrowing score (Spearman’s ρ = −0.22, P < 0.001).

Multivariable logistic regression analysis showed significantly lower odds of an elevated vdHS score (vdHS > 10) in subjects with greater BMI, adjusted for baseline age, sex, race, smoking history, albumin, GFR, ESR, CCP status, CS use, disease duration and disease activity measured by DAS-28(CRP) (Table 2). There was a progressively lower risk of an elevated vdHS score with each ascending category of BMI. Compared with normal weight individuals, obese patients had a lower risk (OR = 0.40, 95% CI 0.22, 0.74, P = 0.003), whereas there was a significantly higher risk in underweight patients (OR = 3.86, 95% CI 1.66, 9.00, P = 0.002). An elevated BMI (BMI > 25 kg/m²) was associated with a significantly lower risk of an elevated vdHS score (OR = 0.43, 95% CI 0.27, 0.67, P < 0.001) compared with those below that cut-off. A similar trend existed in both components of the vdHS score (Table 2). An elevated BMI (>25 kg/m²) was associated with a lower risk of an elevated erosion score (OR = 0.41, 95% CI 0.25, 0.66, P < 0.001) and joint-space narrowing score (OR = 0.30, 95% CI 0.17, 0.52, P < 0.001). In a predictive linear regression model, variables significantly associated with greater vdHS score included higher age, lower BMI, greater swollen joint count and tender joint count, greater ESR, CCP positivity and longer disease duration.

Disability

In contrast to the negative association between BMI and RJD, the odds of having an elevated HAQ score were higher in patients with higher BMI (Table 2). BMI was modestly correlated with HAQ score (Spearman’s ρ = −0.10, P = 0.02). A BMI > 25 kg/m² was associated with a greater risk of an elevated HAQ score (>1) (OR = 2.08, 95% CI 1.23, 3.52, P = 0.006) in linear regression analysis, controlling for the above variables. Obese patients on average had a 0.16 (95% CI 0.03, 0.30) higher HAQ score than normal weight subjects (P = 0.018).
Data are presented as mean (SD) or median (interquartile range) if skewed. There was no evidence of effect modification (and in all racial groups (Fig. 2). Analysis of subgroups showed that the effect of multiple risk factors was additive and linear, there was significant effect modification by the number of modifiable risk factors present in each subject ($P = 0.05$).

Subgroup with adipokine levels

Adiponectin and leptin levels were available in 100 subjects. There was a negative correlation between BMI and adiponectin levels (Spearman’s $\rho = -0.28$, $P = 0.004$) and leptin levels (Spearman’s $\rho = -0.62$, $P < 0.0001$). Leptin levels, but not adiponectin levels, correlated with vdHS scores ($P = 0.03$).

Adiponectin was not significantly associated with vdHS scores in multivariable models controlling for BMI. Similarly, the association between BMI and vdHS score did not change with addition of adiponectin to the model (Table 3). In multivariable linear regression there was a significant negative association between leptin levels (per 1 μg/ml) and natural log-adjusted vdHS scores after adjustment for age, sex, race, DAS-28(CRP), disease duration, smoking, GFR and CCP status [$\beta = -0.020$ (95% CI $-0.040$, $-0.0011$), $P = 0.04$]. This association was no

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**Table 1** Characteristics of study subjects by BMI category at baseline

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Underweight (&lt;20 kg/m²)</th>
<th>Normal (20-24.9 kg/m²)</th>
<th>Overweight (25-29.9 kg/m²)</th>
<th>Obese (≥30 kg/m²)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>41 (8.2)</td>
<td>156 (31.2)</td>
<td>175 (35.1)</td>
<td>127 (25.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Age, years</td>
<td>41.5 (12.7)</td>
<td>47.6 (13.6)</td>
<td>52.2 (10.4)</td>
<td>50.8 (11.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex: female, %</td>
<td>85.4</td>
<td>85.9</td>
<td>81.1</td>
<td>82.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>69.9</td>
<td>41.5</td>
<td>75.4</td>
<td>85.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian, %</td>
<td>25</td>
<td>53.7</td>
<td>13.7</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Black, %</td>
<td>0</td>
<td>2.4</td>
<td>1.1</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Smoking, %</td>
<td>19.5</td>
<td>28.9</td>
<td>37.1</td>
<td>39.8</td>
<td>0.038</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>3.9 (0.37)</td>
<td>4.2 (0.42)</td>
<td>4.2 (0.33)</td>
<td>4.2 (0.32)</td>
<td>0.0006</td>
</tr>
<tr>
<td>GFR, ml/min/1.73 m²</td>
<td>109 (23.3)</td>
<td>93.5 (19.9)</td>
<td>85.1 (20.1)</td>
<td>83.7 (19.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>63.5 (40, 40)</td>
<td>40 (25, 60)</td>
<td>38 (20, 60)</td>
<td>35 (24, 51)</td>
<td>0.0005</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>2.4 (1.4, 1.4)</td>
<td>1.4 (0.4, 4.1)</td>
<td>1.3 (0.5, 2.8)</td>
<td>0.9 (0.5, 2.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>RF positive, %</td>
<td>78.2</td>
<td>78.1</td>
<td>75.9</td>
<td>63.8</td>
<td>0.03</td>
</tr>
<tr>
<td>CCP positive, %</td>
<td>80.1</td>
<td>78.1</td>
<td>77.7</td>
<td>62.5</td>
<td>0.004</td>
</tr>
<tr>
<td>CS use, %</td>
<td>51.2</td>
<td>54.5</td>
<td>52.6</td>
<td>54.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>1.4 (0.6-2.9)</td>
<td>1.15 (0.6-4.4)</td>
<td>1.2 (0.5-4.7)</td>
<td>1.3 (0.5-3.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pain score</td>
<td>6.4 (5.1-7.6)</td>
<td>6.25 (4.5-7.7)</td>
<td>7.1 (5.2-8.2)</td>
<td>6.7 (5.4-8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>20 (13-38)</td>
<td>24.5 (13-37)</td>
<td>24 (15-38)</td>
<td>28 (16-38)</td>
<td>0.3</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>13 (6-25)</td>
<td>12 (8-19)</td>
<td>13 (8-22)</td>
<td>13 (8-19)</td>
<td>0.7</td>
</tr>
<tr>
<td>DAS-28(CRP)</td>
<td>6.54 (1.14)</td>
<td>6.24 (1.13)</td>
<td>6.23 (1.18)</td>
<td>6.28 (1.15)</td>
<td>0.5</td>
</tr>
<tr>
<td>DAS-28(CRP)</td>
<td>5.81 (1.11)</td>
<td>5.70 (1.08)</td>
<td>5.75 (1.06)</td>
<td>5.74 (1.03)</td>
<td>0.9</td>
</tr>
<tr>
<td>HAQ score</td>
<td>1.4 (0.55)</td>
<td>1.5 (0.69)</td>
<td>1.6 (0.64)</td>
<td>1.6 (0.67)</td>
<td>0.08</td>
</tr>
<tr>
<td>GDPT</td>
<td>6.5 (5.2-7.5)</td>
<td>5.7 (4.7-7.8)</td>
<td>6.3 (4.8-8.1)</td>
<td>6.5 (4.9-8)</td>
<td>0.5</td>
</tr>
<tr>
<td>GDEV</td>
<td>6.4 (5.7-8.6)</td>
<td>6.05 (4.6-7.3)</td>
<td>6.3 (5.2-7.7)</td>
<td>6.2 (5.2-7.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>vdHS</td>
<td>14.5 (4.5-47.5)</td>
<td>7.0 (2-27.5)</td>
<td>5.5 (2.5-20)</td>
<td>4.5 (1.5-11)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Erosion score</td>
<td>8 (3-22.5)</td>
<td>4.5 (1.5-16.9)</td>
<td>4.5 (2.13-2.2)</td>
<td>4 (1.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Joint-space narrowing score</td>
<td>6 (2-23)</td>
<td>1.5 (0-10.5)</td>
<td>1 (0-7)</td>
<td>0 (0-2.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Subset: n = 100</td>
<td>n = 9</td>
<td>n = 35</td>
<td>n = 37</td>
<td>n = 19</td>
<td></td>
</tr>
<tr>
<td>Adiponectin, μg/ml</td>
<td>4.29 (1.91)</td>
<td>3.85 (1.66)</td>
<td>3.41 (1.58)</td>
<td>3.30 (2.40)</td>
<td>0.1</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>4.17 (3.69)</td>
<td>9.31 (6.29)</td>
<td>16.13 (11.66)</td>
<td>33.05 (17.25)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean (s.d.) or median (interquartile range) if skewed. P-value is shown for ANOVA and Kruskal-Wallis tests of significance across BMI category. GDPT: global patient assessment; GDEV: global evaluator assessment.
Baseline BMI category was not significantly associated with risk of radiographic progression of joint damage at 1 year of follow-up. This was in contrast to previous studies with risk of radiographic progression of joint damage at 1 year of follow-up [4, 5]. This observation is potentially due to the very small degree of progression potentially due to the very small degree of progression among those with erosions at baseline (P > 0.2), but median change was greater among those who did not have progression of erosions on radiographs at 52 weeks (P = 0.22, 0.92) vs 0 (95% CI –0.38, 0.68, P = 0.02). There was a trend toward a higher proportion with progression among subjects who lost weight (P = 0.07). In a multivariable logistic regression model, there was no significant association between a change in BMI (per 1 kg/m²) over the first 24 weeks and a progression of vdHS (OR = 0.94 (95% CI 0.84, 1.06) P = 0.3) after adjusting for age, race, sex, baseline BMI, treatment group, DAS-28(CRP) at baseline and CCP status. Similarly, a loss of BMI at 24 weeks was not independently associated with an increased risk or progression [OR = 1.44 (95% CI 0.90, 2.28), P = 0.1].

Discussion

Our study confirms prior observations that BMI is independently associated with a lower prevalence of RJD in subjects with RA. Contrary to previous reports, the association was present in all evaluated subgroups in our study, including CCP-negative subjects and those with longer disease duration. Previous findings may be explained by differences in study populations, including lower rates of joint destruction in seronegative subjects, resulting in a lack of power to show an association in this subgroup [4, 5].

An extensive number of potential confounding factors were examined. Subjects with greater BMI had significantly higher rates of active smoking, a behaviour typically thought to be associated with more severe disease. GFR was lower in patients with higher BMI, a finding that is likely due to the use of the MDRD equation, which may underestimate GFR in patients with higher BMI [16]. Underweight patients had significantly higher ESR and CRP levels and were more likely to be seropositive. In multivariable regression, the association between BMI and the presence of erosions remained strong even when adjusting for all of these variables.

Baseline BMI category was not significantly associated with risk of radiographic progression of joint damage at 1 year of follow-up. This is in contrast to previous studies with longitudinal follow-up [4, 5]. This observation is potentially due to the very small degree of progression.
present in our cohort over a 1-year period compared with other study populations, or it could represent a true negative finding. Similarly, changes in BMI were not clearly associated with radiographic changes. Studies with longer follow-up and more sensitive outcome measures are necessary to more accurately assess the progression of joint damage.

Despite the negative association between BMI and joint destruction, greater BMI was associated with higher pain scores and higher levels of disability in our cohort, as

Association of BMI alone (Model 1), adiponectin alone (Model 2) and both variables (Model 3) with normalized, log-adjusted vdHS scores after multivariable adjustment. aAlso adjusted for age, sex, race, smoking history, GFR, CCP status, DAS-28(CRP) and disease duration. bSimilar results were found when controlling for interaction between BMI and risk factors for bone loss.

Table 3: Multivariable linear regression analysis of 100 subjects with adiponectin levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1a,b (R^2 = 0.40)</th>
<th>Model 2a (R^2 = 0.38)</th>
<th>Model 3a,b (R^2 = 0.41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P-value</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>BMI (per 1 kg/m^2)</td>
<td>-0.064 (-0.12, -0.030)</td>
<td>0.04</td>
<td>-0.059 (-0.12, 0.0027)</td>
</tr>
<tr>
<td>Adiponectin (per 1 µg/ml)</td>
<td>-0.13 (-0.030, 0.30)</td>
<td>0.10</td>
<td>0.097 (-0.068, 0.26)</td>
</tr>
</tbody>
</table>

Table 4: Proportion of subjects with radiographic progression (defined as vdHS score increase of >0.5) at 52 weeks by BMI category

<table>
<thead>
<tr>
<th>Radiographic outcome</th>
<th>Underweight (&lt;20 kg/m^2)</th>
<th>Normal (20-24.9 kg/m^2)</th>
<th>Overweight (25-29.9 kg/m^2)</th>
<th>Obese (≥30 kg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No progression, n (%)</td>
<td>27 (66)</td>
<td>98 (67)</td>
<td>120 (75)</td>
<td>87 (76)</td>
</tr>
<tr>
<td>Progression, n (%)</td>
<td>14 (34)</td>
<td>48 (33)</td>
<td>41 (25)</td>
<td>27 (24)</td>
</tr>
</tbody>
</table>

Pearson χ^2 = 4.04, P = 0.3.
measured by the HAQ. This is likely due to the comorbid conditions associated with obesity, as the HAQ score is highly influenced by comorbidities [17]. This finding suggests that the apparent protective effect of greater BMI does not necessarily translate into improved morbidity, at least in the short term.

The mechanism by which BMI is associated with RJD is unknown. BMI may be a reflection of disease burden, with severe disease leading to weight loss and cachexia. Rheumatoid cachexia more typically results in loss of lean body mass with unchanged or increased adiposity and weight [17, 18]. This study and others have extensively controlled for measures associated with disease burden such as DAS-28 and inflammatory markers, therefore confounding by disease severity has not explained the association. Despite this, BMI might simply be a more sensitive marker of disease burden than other existing markers. These results suggest that more attention to weight (and perhaps changes in weight) is warranted when predicting risk in RA. More attention to body composition in future studies is also critical to clarify this issue.

Alternatively, the endocrine function of adipose tissue could modulate the disease. There has been interest in the role of adipokines [18]; however, a causal role for adipokines in RA remains speculative [19, 20]. Adiponectin is an appealing candidate—its expression is typically lower in patients with a higher BMI, and levels have been shown to increase with weight loss [21, 22]. Serum levels are elevated in RA [19, 23], and higher levels of adiponectin have previously been associated with radiographic joint destruction [24, 25]. This adipokine may lead to increased production of synovial VEGF and MMPs and cause matrix destruction [26]. We found that adiponectin was not associated with vdHS scores and did not confound the association between BMI and joint damage. Our data suggest that BMI is independently associated with radiographic damage through a mechanism that may be independent of adiponectin. Leptin levels appear to associate with BMI and joint damage; however, in multivariable analysis it appears that leptin is co-linear with BMI and does not independently associate with erosion scores. Longitudinal data may help to clarify these associations.

The increased mechanical load imposed by higher BMI could also directly result in increased bone synthesis, protecting against joint destruction. In the general population, obesity is associated with decreased rates of osteoporosis [27, 28], a finding that could be due to mechanical loading forces [10], peripheral production of oestrogens in adipose tissue [29] or other unidentified mechanisms. Interestingly, in our study, subjects who had multiple risk factors for bone loss had a greater protective effect of BMI on joint destruction, while the effect was absent in subjects who had none of these risk factors. This finding is hypothesis generating.

We utilized a large cohort of patients with rigorous collection of an extensive set of potential confounding variables, allowing for a well-powered multivariable analysis of this relationship. There are several limitations. Body composition is variable among different populations and the BMI cut-offs chosen may not be ideal for all racial groups. Furthermore, very few patients of African descent were represented in this study. Dietary information was limited and waist circumference was not available. BMI may be a poor measure in inflammatory disease, and thus direct measures of body composition may be needed to define the link between adiposity, inflammation and joint destruction in RA. Finally, minimal progression of joint damage during the study and the lack of longer term follow-up limit prospective analysis.

In summary, we confirmed an association between BMI and prevalent joint destruction in RA and have shown this association is consistent in all subgroups evaluated, including both seropositive and seronegative subjects. Neither adiponectin nor leptin levels adequately explain this association in a limited subset. The effect was modified by risk factors for bone loss, suggesting another potential mechanism for a protective effect of greater weight.

Rheumatology key messages
- Greater body mass was associated with less prevalent radiographic joint disease in all RA subgroups.
- Adipokine levels do not appear to mediate the association between body mass and radiographic damage.
- Baseline BMI was not significantly and independently associated with radiographic progression at 52 weeks.

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