

## CONCISE REPORT

## Obesity and rates of clinical remission and low MRI inflammation in rheumatoid arthritis

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► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2017-211569>).

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Received 30 March 2017

Revised 9 May 2017

Accepted 10 May 2017

Published Online First

12 June 2017



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**To cite:** George MD, Østergaard M, Conaghan PG, et al. *Ann Rheum Dis* 2017;**76**:1743–1746.

**ABSTRACT**

**Objectives** Obesity has been proposed as a risk factor for refractory rheumatoid arthritis (RA). We evaluated the impact of obesity on achieving clinical and imaging definitions of low disease activity.

**Methods** This study evaluated 470 patients with RA from GO-BEFORE and GO-FORWARD randomised clinical trials. Included patients had blinded clinical disease activity measures and MRI at baseline, 24 and 52 weeks. Synovitis, osteitis and total inflammation scores were determined using the RA MRI scoring system. Multivariable logistic regression analyses compared odds of achieving Disease Activity Score using 28 joints and C-reactive protein (DAS28-CRP) remission, low component measures, or low MRI inflammation measures at 24 weeks in patients with obesity versus no obesity.

**Results** At 24 weeks, patients with obesity were significantly less likely to achieve DAS28(CRP) remission (OR 0.47; 95% CI 0.24 to 0.92,  $p=0.03$ ). In contrast, patients with obesity had similar odds of achieving low synovitis (OR 0.94; 95% CI 0.51 to 1.72,  $p=0.84$ ) and inflammation scores (OR 1.16; 95% CI 0.61 to 2.22,  $p=0.64$ ) and greater odds of achieving low osteitis scores (OR 2.06; 95% CI 1.10 to 3.84,  $p=0.02$ ) versus normal weight patients.

**Conclusions** Patients with RA and obesity have lower rates of DAS28 remission but similar rates of low MRI activity compared with patients without obesity, suggesting that obesity and its associated comorbidities can bias clinical disease activity measures.

**Trial registration number** NCT00361335 and NCT00264550; Post-results.

**INTRODUCTION**

Obesity is one of the most common comorbid conditions among patients with rheumatoid arthritis (RA). Numerous studies have suggested that patients with obesity have a poorer response to treatment and lower likelihood of achieving RA disease remission.<sup>1–6</sup> While some have concluded that obesity is associated with more refractory RA, an alternative explanation is that obesity and its related symptoms and comorbidities directly influence and bias specific components of disease activity measures.<sup>7</sup>

MRI can be used to assess both damage and inflammatory activity in RA. MRI measured synovitis and osteitis (bone oedema) are sensitive to change and have been used as outcome measures in clinical trials. These measures are also predictive

of progressive joint damage independent of clinical disease activity.<sup>8–10</sup> Recently, thresholds for low MRI activity have been defined and validated using RA MRI scores (RAMRIS). These thresholds identify patients unlikely to have structural progression, even if definitions of clinical remission are not met.<sup>10</sup>

The objective of this study was to compare the impact of obesity on attaining different clinical and imaging definitions of low activity and remission. We hypothesised that patients with obesity would be less likely to attain clinical remission but equally likely to meet MRI definitions of low activity versus patients without obesity.

**METHODS**

The study population comes from secondary analysis of the GO-BEFORE (Golimumab Before Employing Methotrexate as the First-Line Option in the Treatment of Rheumatoid Arthritis of Early Onset; Clinicaltrials.gov identifier NCT00361335) and GO-FORWARD (Golimumab in Active Rheumatoid Arthritis Despite Methotrexate Therapy; NCT00264550) randomised, multi-centre, double-blind, placebo-controlled trials, which evaluated the efficacy of tumour necrosis factor- $\alpha$  antagonist golimumab for the treatment of RA. Both studies compared golimumab in combination with methotrexate with methotrexate or golimumab monotherapy. GO-BEFORE studied methotrexate-naïve patients and GO-FORWARD studied patients with inadequate methotrexate response. Detailed methods and results of both studies have previously been published.<sup>11 12</sup> The trials were conducted according to the Declaration of Helsinki. The secondary analysis of deidentified trial data was considered exempt by the Internal Review Board at the University of Pennsylvania.

This analysis includes the subset of patients in both studies who had MRIs scored for synovitis, osteitis, and/or bone erosion at baseline and during follow-up. Patients aged  $\geq 18$  years who met the American College of Rheumatology (ACR) 1987 criteria for RA and had active disease were recruited into the MRI substudy at participating sites. Data collection at each 4-week visit through 52 weeks included blinded assessments of disease activity score in 28 joints (DAS28(C reactive protein (CRP))) and Health Assessment Questionnaire (HAQ). MRI was performed at baseline, week 24 and week 52. Body mass index (BMI) at baseline was calculated as weight in kilograms divided by height in metres squared, and categorised as

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**Table 1** Baseline characteristics of the study population by BMI group

	BMI <20, n=51	BMI 20 to <25, n=164	BMI 25 to <30, n=152	BMI ≥30, n=103	p Value
Female	43 (84%)	136 (83%)	126 (83%)	87 (84%)	0.98
Age, years	44±14	47±12	51±11	52±11	<0.001
Race					
White	15 (29%)	92 (56%)	106 (70%)	87 (84%)	<0.001
Black	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0.61
Asian	35 (69%)	61 (37%)	25 (16%)	7 (7%)	<0.001
Other	1 (2%)	11 (7%)	20 (13%)	8 (8%)	0.05
GO-BEFORE	26 (51%)	94 (57%)	89 (59%)	61 (59%)	0.78
GO-FORWARD	25 (49%)	70 (43%)	63 (41%)	42 (41%)	0.78
CCP positive	39 (76%)	136 (83%)	121 (80%)	75 (73%)	0.25
DAS28(CRP)	5.5±1.2	5.3±1.1	5.6±1.1	5.5±1.0	0.06
Swollen joint count	8.9±6.0	8.7±5.1	9.9±5.8	9.7±5.8	0.19
Tender joint count	12.2±7.4	11.5±6.9	14.4±7.5	13.8±7.0	0.002
Patient global	6.3±2.4	5.7±2.4	6.0±2.4	6.0±2.2	0.41
HAQ	1.3±0.7	1.3±0.7	1.6±0.7	1.7±0.7	<0.001
CRP, mg/dL	1.2 (0.4–3.6)	1.0 (0.3–2.4)	0.9 (0.4–2.3)	0.9 (0.4–2.0)	0.59
RAMRIS scores at baseline					
Synovitis	7.9 (4.5–13.5)	8.0 (4.3–12.0)	9.0 (5.0–12.5)	7.5 (4.0–10.8)	0.07
Osteitis	8.0 (1.0–19.5)	8.0 (1.5–18.4)	4.5 (1.4–10.1)	3.0 (0.5–9.0)	<0.001
Inflammation	26.2 (10.1–46.6)	28.8 (8.6–50.2)	21.0 (11.0–32.8)	14.5 (7.4–30.0)	0.003
Bone erosion	14.5 (8.7–37.0)	16.4 (9.0–40.0)	14.0 (9.5–22.5)	13.5 (8.3–20.0)	0.02

Mean±SD compared with ANOVA, median (IQR) compared with Kruskal-Wallis, proportions compared with  $\chi^2$ .

BMI, body mass index; DAS28(CRP), disease activity score using 28 joints and CRP; CCP, citrullinated peptide; CRP, C reactive protein; RAMRIS, rheumatoid arthritis MRI scores.

BMI <20 (underweight), BMI 20 to <25 (normal weight), BMI 25 to <30 (overweight) and BMI ≥30 (obese).

MRIs of the dominant wrist and second to fifth metacarpophalangeal joints were obtained using a 1.5 T MRI with contrast enhancement as previously described and scored by two independent blinded readers using the RAMRIS scoring system.<sup>9</sup> Low synovitis and low osteitis scores were defined as ≤3 based on recently defined thresholds.<sup>10</sup> Inflammation scores were calculated by adding the synovitis score to twice the osteitis score as previously described, with a low score defined as ≤9.<sup>10</sup>

Clinical remission was defined as a DAS28(CRP) score <2.6. Thresholds for a low swollen joint count, tender joint count, patient global score and CRP in mg/dL were all defined as ≤1 and low HAQ as ≤0.5 as defined in the 2011 ACR/European League Against Rheumatism Boolean definitions of remission.<sup>13</sup>

Data were analysed with STATA V.13.1 software (StataCorp, College Station, Texas, USA). Differences in demographics, disease activity and MRI measures at baseline across BMI categories were evaluated with  $\chi^2$ , ANOVA and Kruskal-Wallis tests. In the primary analysis, multivariable logistic regression models evaluated the association between BMI category (normal BMI as the reference) and each of the 24-week clinical disease activity or imaging outcomes, adjusting for age, sex, race, anticyclic citrullinated peptide (CCP) antibody status, study and treatment assignment. The probability of reaching low activity thresholds was determined from these models for each BMI category at the means of all covariates and displayed graphically. Secondary analysis evaluated the same outcomes at 52 weeks.

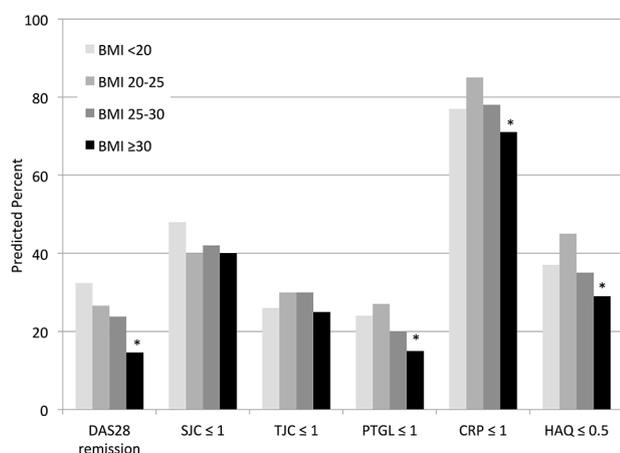
## RESULTS

Baseline characteristics of the 470 patients in the cohort are shown in [table 1](#). Overweight and patients with obesity were older and more often white. Overweight and patients with obesity had higher tender joint counts and worse HAQ scores at baseline, although DAS28(CRP) scores were similar across BMI

categories. As has been previously published from this cohort, overweight and patients with obesity had substantially lower osteitis (bone oedema) scores and fewer erosions at baseline ([table 1](#)).<sup>14</sup>

At 24 weeks, DAS28(CRP) remission was present in 28% of underweight, 28% of normal weight, 27% of overweight, but only 17% of patients with obesity. After adjustment, patients with obesity were less likely to achieve DAS28(CRP) remission (OR 0.47; 95% CI 0.24 to 0.92,  $p=0.03$ ) or a low HAQ (OR 0.49; 95% CI 0.28 to 0.89,  $p=0.02$ ) compared with normal weight patients ([figure 1](#)) (see online supplementary table 1). Results using Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) or Boolean remission were similar, although not statistically significant (see online supplementary figure 1). Patients with obesity were also less likely to have a favourable patient global score ≤1 (OR 0.47; 95% CI 0.24 to 0.92,  $p=0.03$ ) and less likely to have a CRP ≤1 mg/dL (OR 0.44; 95% CI 0.23 to 0.84,  $p=0.01$ ) at 24 weeks. Results were similar with adjustment for baseline DAS28(CRP) (not shown).

In contrast, low synovitis scores ≤3 and low inflammation scores ≤9 on MRI occurred at similar rates across BMI groups, while low osteitis (bone oedema) scores were more common in patients with obesity (69% of patients with obesity vs 50% of normal weight patients,  $p=0.02$ ). In multivariable models, patients with obesity were not less likely to have low synovitis (OR 0.94; 95% CI 0.51 to 1.72,  $p=0.84$ ) or low inflammation scores (OR 1.02; 95% CI 0.53 to 1.96,  $p=0.95$ ) at 24 weeks versus normal weight patients ([figure 2](#)) (see online supplementary table 2). Patients with obesity were more likely to achieve a low osteitis score compared with normal weight patients (OR 2.06; 95% CI 1.10 to 3.84,  $p=0.02$ ). The odds of a low osteitis score was similar across BMI categories after adjusting for baseline osteitis (obese vs normal weight OR 1.01; 95% CI 0.40 to 2.51,  $p=0.99$ ).

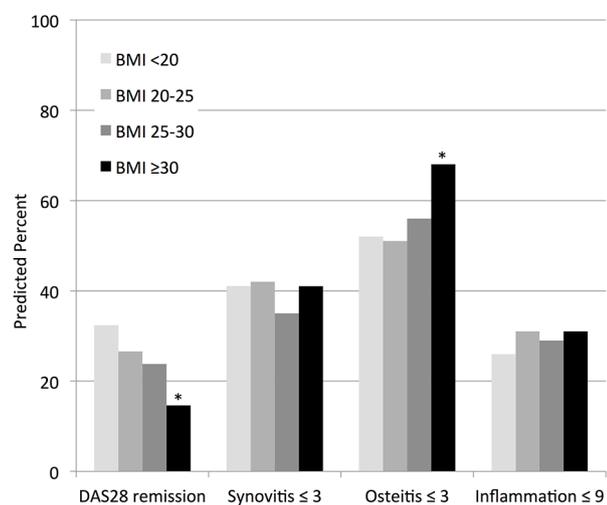


**Figure 1** Rates of low disease activity measures at 24 weeks among different BMI groups. Predicted probabilities were obtained from multivariable logistic regression models at the means of age, sex, race, cyclic citrullinated peptide antibody status, study, treatment assignment. \* $p < 0.05$ . BMI, body mass index; DAS28, disease activity score in 28 joints using CRP; SJC, swollen joint count; TJC, tender joint count; PTGL, patient global visual analogue scale score; CRP, C reactive protein; HAQ, Health Assessment Questionnaire.

Analyses at 52 weeks were similar except that patients with obesity were significantly less likely to have a low tender joint count versus normal weight patients (OR 0.47; 95% CI 0.27 to 0.82,  $p = 0.01$ ) and differences in achieving low HAQ were not significant (see online supplementary table 2).

## DISCUSSION

Obesity was associated with a lower likelihood of achieving DAS28 remission among patients with RA enrolled in these clinical trials. In contrast, these same patients with obesity achieved low MRI activity at a similar rate compared with patients without obesity. These results suggest that obesity is not associated with



**Figure 2** Rates of low clinical disease activity or low MRI scores at 24 weeks among different BMI groups. Predicted probabilities were obtained from multivariable logistic regression models at the means of age, sex, race, cyclic citrullinated peptide antibody status, study, treatment assignment. \* $p < 0.05$ . BMI, body mass index; DAS28, disease activity score in 28 joints using C reactive protein.

more severe or refractory RA, but rather that obesity may bias clinical disease activity measures and thereby reduce the likelihood of achieving remission based on clinical assessments.

Patients with obesity were less likely to have low DAS28 scores at 24 and 52 weeks. Patients with obesity were also less likely to achieve a low patient global score, tender joint count, CRP level and HAQ. These results support previous studies demonstrating that patients with RA and obesity have worse subjective disease activity measures at baseline and poorer response of these subjective measures to treatment.<sup>3 4 15 16</sup> Inflammatory markers such as CRP, although considered more objective, may also be elevated in patients with obesity independent of RA disease activity.<sup>17</sup>

In contrast, patients with obesity had similar rates of achieving a low MRI synovitis or total inflammation score and higher rates of achieving a low osteitis score at 24 and 52 weeks (similar rates when controlling for baseline osteitis). These observations are supported by previous studies showing that obesity is associated with a lower risk of radiographic and MRI joint damage progression.<sup>14 18 19</sup> This study provides new evidence that obesity is not associated with more severe or refractory disease by showing that patients with obesity achieve similar rates of low MRI disease activity despite apparent differences in clinical responses.

This study uses clinical trial data that include rigorous assessment of clinical disease activity measures and blinded MRI scoring at regular intervals. A 'gold standard' assessment of disease activity does not exist and MRI may not capture all aspects of RA disease activity. MRI does, however, provide an objective measure of inflammatory joint disease, a key and defining feature of RA. While very low levels of synovitis or osteitis may be common and non-specific,<sup>20</sup> our use of validated cut-off scores that identify an informative degree of inflammatory disease is an advance over previous literature. Residual confounding by unmeasured factors is also possible in this observational study, although adjustment for baseline demographics, race, CCP antibody positivity and baseline disease activity did not substantially impact the results.

In conclusion, although patients with RA and obesity are less likely to achieve DAS28 remission, these patients have similar rates of achieving low MRI activity. This study addresses an ongoing controversy about the impact of obesity on RA disease activity and suggests that obesity is not associated with more refractory RA. These results highlight the critical role of the clinician, whose challenge is to recognise the importance and limitations of disease activity measures and to consider the impact of comorbidities on disease activity scores and symptoms.

**Acknowledgements** Dr George was supported by the Rheumatology Research Foundation Scientist Development Award. Dr Baker would like to acknowledge the support of a Veterans Affairs Clinical Science Research & Development Career Development Award (IK2 CX000955). The contents of this work do not represent the views of the Department of the Veterans Affairs or the US Government. PE and PGC are supported in part by the National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

**Contributors** All authors were involved in the study design, data collection and interpretation and approved the final version of the manuscript. MG and JB performed the statistical analyses and wrote the manuscript with input from the coauthors.

**Competing interests** PGC has done speakers bureaus or consultancies for AbbVie, BMS, Janssen, Lilly, Novartis, Pfizer and Roche. PE has received consulting fees, speaking fees and/or honoraria from Pfizer, Merck, AbbVie, UCB, Roche, BMS, Lilly and Novartis (less than US\$10,000 each). DGB is an employee of Janssen Biotech. M Østergaard has received fees for consultancy or speaker fees and/or research support from Abbott, AbbVie, BMS, Boehringer-Ingelheim, Celgene, Centocor, Eli-Lilly, GlaxoSmithKline, Hospira, Janssen, Merck, Mundipharma, Novartis,

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Novo, Orion, Pfizer, Regeneron, Sanofi, Schering-Plough, Roche, UCB, Takeda and Wyeth.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Ann Rheum Dis* 2017 76: 1743-1746 originally published online June 12, 2017

doi: 10.1136/annrheumdis-2017-211569

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