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Obesity and Rates of Clinical Remission and Low Magnetic Resonance Imaging Inflammation in Rheumatoid Arthritis

Michael George, MD, MSCE²

Mikkel Østergaard, MD, PhD, DMSc^{4,5}

Philip G. Conaghan, MD, PhD⁶

Paul Emery, MD⁶

Daniel G. Baker, MD⁷

Joshua F. Baker, MD, MSCE^{1,2,3}

1. Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA
2. University of Pennsylvania, School of Medicine, Philadelphia, PA, USA
3. Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA
4. Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark
5. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen Denmark.
6. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds UK
7. Janssen Research & Development, LLC., Horsham PA, USA

Corresponding Author:

Michael George, MD MSCE

Hospital of the University of Pennsylvania

Division of Rheumatology

5 White Building, 3400 Spruce St

Philadelphia, PA 19104

Phone: 215-662-2789

Fax: 215-662-4500

Email: michael.george@uphs.upenn.edu

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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 randomized clinical trials. Included patients had blinded clinical disease activity measures and magnetic resonance imaging (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 [DAS28(CRP)] remission, low component measures, or low MRI inflammation measures at 24 weeks in obese versus non-obese patients.

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

Conclusions: Obese patients with RA have lower rates of DAS28 remission but similar rates of low MRI activity compared to non-obese patients, suggesting that obesity and its associated comorbidities can bias clinical disease activity measures.

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.[1–6] 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.[7]

Magnetic resonance imaging (MRI) can be used to assess both damage and inflammatory activity in RA. MRI measured synovitis and osteitis (bone edema) 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.[8–10] Recently, thresholds for low MRI activity have been defined and validated using RA magnetic resonance imaging scores (RAMRIS). These thresholds identify patients unlikely to have structural progression, even if definitions of clinical remission are not met.[10]

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 hypothesized that obese patients would be less likely to attain clinical remission but equally likely to meet MRI imaging definitions of low activity versus non-obese patients.

METHODS

The study population comes from secondary analysis of the GO-BEFORE (Clinicaltrials.gov identifier NCT00361335) and GO-FORWARD (NCT00264550) randomized, multicenter, double-blind, placebo-controlled trials which evaluated the efficacy of tumor necrosis factor alpha (TNFa) antagonist golimumab for the treatment of RA. Both studies compared golimumab in combination with methotrexate to 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.[11,12] The trials were conducted according to the Declaration of Helsinki. The secondary analysis of de-identified 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 ≥ 18 years old who met American College of Rheumatology 1987 criteria for RA and had active disease were recruited into the MRI sub-study at participating sites. Data collection at each 4-week visit through 52 weeks included blinded assessments of Disease Activity Score in 28 joints [DAS28(CRP)] and Health Assessment Questionnaire (HAQ). MRI was performed at baseline, week 24, and week 52. Body mass index at baseline was calculated as weight in kilograms divided by height in meters squared, and

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

MRIs of the dominant wrist and 2nd-5th metacarpophalangeal (MCP) joints were obtained using a 1.5T MRI with contrast enhancement as previously described and scored by two independent blinded readers using the RAMRIS scoring system.[9] Low synovitis and low osteitis scores were defined as ≤3 based on recently defined thresholds.[10] Inflammation scores were calculated by adding the synovitis score to twice the osteitis score as previously described, with a low score defined as ≤9.[10]

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/EULAR Boolean definitions of remission.[13]

Data was analyzed with STATA 13.1 software (*StataCorp, LP, College Station, TX*).

Differences in demographics, disease activity, and MRI measures at baseline across BMI categories were evaluated with Chi-square, 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, anti-cyclic 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 obese patients were older and more often white. Overweight and obese patients 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 obese subjects had substantially lower osteitis (bone edema) scores and fewer erosions at baseline (**Table 1**).[14]

At 24 weeks, DAS28(CRP) remission was present in 28% of underweight, 28% of normal weight, 27% of overweight, but only 17% of obese patients. After adjustment, obese patients were less likely to achieve DAS28(CRP) remission [OR (95% CI): 0.47 (0.24-0.92), $p=0.03$] or a low HAQ [OR: 0.49 (0.28-0.89), $p=0.02$] compared to normal weight patients (**Figure 1**) (**Supplemental Table 1**). Results using SDAI, CDAI, or Boolean remission were similar although not statistically significant (**Supplemental Figure 1**).

Obese patients were also less likely to have a favorable patient global score ≤ 1 [OR: 0.47 (0.24-0.92), $p=0.03$] and less likely to have a CRP ≤ 1 mg/dL [OR: 0.44 (0.23-0.84), $p=0.01$] 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 edema) scores were more common in obese patients (69% of obese versus 50% of normal weight patients, $p=0.02$). In multivariable models, obese patients were not less likely to have low synovitis [OR: 0.94 (0.51-1.72), $p=0.84$] or low inflammation scores [OR: 1.02 (0.53-1.96), $p=0.95$] at 24 weeks versus normal weight patients (**Figure 2**) (**Supplemental Table 2**). Obese patients were more likely to achieve a low osteitis score compared to normal weight patients [OR: 2.06 (1.10-3.84), $p=0.02$]. The odds of a low osteitis score was similar across BMI categories after adjusting for baseline osteitis (obese versus normal weight OR: 1.01 (0.40-2.51), $p=0.99$).

Analyses at 52 weeks were similar except that obese patients were significantly less likely to have a low tender joint count versus normal weight patients [OR: 0.47 (0.27-0.82), $p=0.01$] and differences in achieving low HAQ were not significant (**Supplemental 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 obese patients achieved low MRI activity at a similar rate compared to non-obese patients. These results suggest that obesity is not associated with 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.

Obese patients 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 RA patients with obesity have worse subjective disease activity measures at baseline and poorer response of these subjective measures to treatment.[3,4,15,16]

Inflammatory markers such as CRP, although considered more objective, may also be elevated in patients with obesity independent of RA disease activity.[17]

In contrast, obese patients 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.[14,18,19] This study provides new evidence that obesity is not associated with more severe or refractory disease by showing that obese patients achieve similar rates of low MRI disease activity despite apparent differences in clinical responses.

This study utilizes clinical trial data that includes 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 nonspecific,[20] our use of validated cutoff 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 obese patients with RA are less likely to achieve DAS28 remission, they 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 recognize the importance and limitations of disease activity measures and to consider the impact of comorbidities on disease activity scores and symptoms.

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DISCLOSURES

MD George and JF Baker have nothing to disclose. PG Conaghan has done speakers bureaus or consultancies for Abbvie, BMS, Janssen, Lilly, Novartis, Pfizer, and Roche. P Emery has received consulting fees, speaking fees, and/or honoraria from Pfizer, Merck, Abbvie, UCB, Roche, BMS, Lilly, and Novartis (less than \$10,000 each). DG Baker is an employee of Janssen Biotech, Inc. M Østergaard has received fees for consultancy or speaker fees and/or research support from Abbott, AbbVie, BMS, Boehringer-Ingelheim, Celgene, Centocor, Eli-Lilly, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo, Orion, Pfizer, Regeneron, Sanofi, Schering-Plough, Roche, UCB, Takeda and Wyeth.

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

	BMI <20 N = 51	BMI 20-<25 N = 164	BMI 25-<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-square.

BMI: body mass index in kg/m². DAS28(CRP): disease activity score using 28 joints and CRP. CRP: C-reactive protein. RAMRIS: rheumatoid arthritis magnetic resonance imaging scores

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 VAS score; CRP = C-reactive protein; HAQ = health assessment questionnaire

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

References

- 1 Klaasen R, Wijbrandts CA, Gerlag DM, *et al.* Body mass index and clinical response to infliximab in rheumatoid arthritis. *Arthritis Rheum* 2011;**63**:359–64. doi:10.1002/art.30136
- 2 Gremese E, Carletto A, Padovan M, *et al.* Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. *Arthritis Care Res* 2013;**65**:94–100. doi:10.1002/acr.21768
- 3 Heimans L, van den Broek M, le Cessie S, *et al.* Association of high body mass index with decreased treatment response to combination therapy in recent-onset rheumatoid arthritis patients. *Arthritis Care Res* 2013;**65**:1235–42. doi:10.1002/acr.21978
- 4 Sandberg MEC, Bengtsson C, Källberg H, *et al.* Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. *Ann Rheum Dis* 2014;**73**:2029–33. doi:10.1136/annrheumdis-2013-205094
- 5 Ellerby N, Matthey DL, Packham J, *et al.* Obesity and comorbidity are independently associated with a failure to achieve remission in patients with established rheumatoid arthritis. *Ann Rheum Dis* 2014;**73**:e74. doi:10.1136/annrheumdis-2014-206254
- 6 Liu Y, Hazlewood GS, Kaplan GG, *et al.* The Impact of Obesity on Remission and Disease Activity in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Arthritis Care Res* Published Online First: 9 May 2016. doi:10.1002/acr.22932
- 7 Peltonen M, Lindroos AK, Torgerson JS. Musculoskeletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. *Pain* 2003;**104**:549–57.
- 8 Østergaard M, Emery P, Conaghan PG, *et al.* Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. *Arthritis Rheum* 2011;**63**:3712–22. doi:10.1002/art.30592
- 9 Baker JF, Ostergaard M, Emery P, *et al.* Early MRI measures independently predict 1-year and 2-year radiographic progression in rheumatoid arthritis: secondary analysis from a large clinical trial. *Ann Rheum Dis* 2014;**73**:1968–74. doi:10.1136/annrheumdis-2013-203444

- 10 Baker JF, Østergaard M, Emery P, *et al.* Development and validation of rheumatoid arthritis magnetic resonance imaging inflammation thresholds associated with lack of damage progression. *Clin Exp Rheumatol* 2017.
- 11 Emery P, Fleischmann RM, Moreland LW, *et al.* Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naïve patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;**60**:2272–83. doi:10.1002/art.24638
- 12 Keystone EC, Genovese MC, Klareskog L, *et al.* Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;**68**:789–96. doi:10.1136/ard.2008.099010
- 13 Felson DT, Smolen JS, Wells G, *et al.* American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;**70**:404–13. doi:10.1136/ard.2011.149765
- 14 Baker JF, Ostergaard M, George M, *et al.* Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years. *Ann Rheum Dis* 2014;**73**:1923–8. doi:10.1136/annrheumdis-2014-205544
- 15 Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. *Arthritis Care Res* 2012;**64**:1471–9. doi:10.1002/acr.21627
- 16 Ajeganova S, Andersson ML, Hafström I, *et al.* Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset. *Arthritis Care Res* 2013;**65**:78–87. doi:10.1002/acr.21710
- 17 George MD, Giles JT, Katz PP, *et al.* The impact of obesity and adiposity on inflammatory markers in patients with rheumatoid arthritis. *Arthritis Care Res* In Press.
- 18 Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. *Arthritis Rheum* 2007;**56**:3575–82. doi:10.1002/art.23033
- 19 van der Helm-van Mil AHM, van der Kooij SM, Allaart CF, *et al.* A high body mass index has a protective effect on the amount of joint destruction in small joints in

early rheumatoid arthritis. *Ann Rheum Dis* 2008;**67**:769–74.
doi:10.1136/ard.2007.078832

- 20 Mangnus L, van Steenbergen HW, Reijniere M, *et al.* Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population. *Arthritis Rheumatol Hoboken NJ* 2016;**68**:2593–602.
doi:10.1002/art.39749