Rheumatoid arthritis: predictors of clinical response to TNF blockade
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CHAPTER 5

Body Mass Index and Clinical Response to Infliximab in Rheumatoid Arthritis

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ABSTRACT

Objective: Adipose tissue has immunomodulating effects in rheumatoid arthritis (RA), although the exact role is at present unclear. We investigated prospectively if body mass index (BMI) affects response to infliximab in RA patients.

Methods: In 89 active RA patients BMI was calculated before initiation of infliximab treatment (3 mg/kg intravenously). After 16 weeks of treatment changes in disease activity were monitored by the disease activity score in 28 joints (DAS28).

Results: Mean BMI was 26 kg/m² (SD 5, range 17–42) and it was positively correlated to baseline DAS28 ($r = 0.34; P = 0.001$). As selecting patients based on DAS28 could influence clinical response to TNF blockade due to regression to the mean, ANCOVA was used to correct for baseline DAS28. A highly significant, negative association between BMI and absolute decrease in DAS28 after 16 weeks ($P = 0.001$) was found.

Conclusion: Although infliximab dosage is based on body weight, RA patients with a high BMI responded less well to infliximab, also when adjusted for baseline DAS28 or ACPA status. These results support the notion that fat tissue may be involved in RA pathophysiology and could have implications for other immune-mediated inflammatory conditions treated with TNF antagonists.
Adipose tissue is not merely fat resting in the body. Nowadays, it is recognized as an active site exerting endocrine and immune effects on multiple other organs through the release of adipocytokines. These factors include leptin, resistin, adiponectin and visfatin, as well as classical cytokines, like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and monocyte chemotactic protein (MCP)-1, which are possibly expressed by inflammatory cells infiltrating fat tissue. Together, these molecules influence immune functions, leading to local and generalized inflammation, which could play a role in the development of several diseases, such as diabetes mellitus, atherosclerosis, rheumatoid arthritis (RA), and osteoarthritis. Although the actions of various cytokines in rheumatoid arthritis, a chronic, immune-mediated inflammatory disease mostly affecting the joints, are largely known, the role of adipose tissue herein remains controversial.

Active disease could lead to weight loss and consequently lower BMI. Other research has shown, however, that fat mass was independently and positively correlated to C-reactive protein (CRP) levels in female patients with RA. Although CRP levels are positively associated with cardiovascular mortality, there was less mortality in obese RA patients. In this latter study, the body mass index (BMI) had a protective effect only when the erythrocyte sedimentation rate (ESR) was low. Moreover, a higher BMI appears to be associated with less severe radiographic joint damage in RA, even in patients with anti-citrullinated peptide antibodies (ACPA) and/or rheumatoid factor (RF). Although these autoantibodies, especially ACPA, are associated with rapidly progressive, erosive disease, this might suggest that adipose tissue is related to milder disease in terms of joint destruction. Taken together, the relationship between BMI and signs and symptoms of RA appears to be complex.

A significant part of RA patients (about 30%) does not respond well to TNF blockers for as yet not fully elucidated reasons. We hypothesize that BMI could affect different responses to treatment in RA patients. Therefore, we examined the relationship between BMI at baseline and the primary clinical response to infliximab in a prospective study. Infliximab was chosen as this TNF blocker is dosed per kilogram body weight.

**PATIENTS AND METHODS**

**Disease characteristics and BMI**

Eighty-nine patients with active RA, according to the American College of Rheumatology criteria were included in this exploratory study. The baseline demographic and clinical features of the patients of the larger prospective single center cohort have been described previously and are summarized in Table 1 for those who were included in the present study. Patients were selected for the analysis presented here based on the availability of BMI, serum at baseline combined with standardized follow up data on the response to infliximab treatment. All study patients used stable dosages of methotrexate (5-30 mg/week), were naïve to biologicals, and had active disease defined by a disease activity score evaluated in 28 joints (DAS28) ≥ 3.2. Use of oral corticosteroids (≤10 mg/day) and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed if the dose had not been changed within one month prior to baseline. Intra-articular steroid injections within the last month were not allowed.

Presence of IgM-RF and ACPA, measured by anti-CCP2 ELISA (Immunoscan RA, Mark2, Euro-Diagnostica NO.RA-96RT, Arnhem, the Netherlands), were assessed at baseline, as well as
presence of erosive joint disease determined by X-ray. Length and body weight measures were taken at baseline, and BMI was calculated by weight in kilograms divided by height in square meters. All patients received infliximab intravenously in a dosage of 3 mg/kg at baseline, week 2 and 6, and subsequently every 8 weeks.

We determined the responder status by reduction in DAS28 after 16 weeks of therapy. RA patients with DAS28 ≥1.2 (twice the measurement error over time) were defined as responders, representing a clinically significant improvement. The dichotomy of the ΔDAS28 (on average comparable with a 20% improvement in DAS28) was chosen, because it is applied in daily clinical practice and required for prolongation of reimbursement for TNF-alpha blocking therapy by insurance companies in the Netherlands. Response was also determined according to the European League against Rheumatism (EULAR) response criteria, which are divided into three categories: good, moderate and non-responders. Clinical response was evaluated at 16 weeks, since a significant improvement is expected to occur within 3-4 months, after which alternative treatment should be considered. All patients gave written informed consent and the study was approved by the Medical Ethics Committee of the Academical Medical Center/University of Amsterdam.

Table 1. Baseline patient characteristics for responders (decrease in DAS28 ≥1.2 after 16 weeks of treatment) and non-responders. Data are represented as mean (SD), median (interquartile range [IQR]) or n (%), as appropriate. Baseline characteristics were compared between responders and non-responders (Chi-square test, independent Student’s t test and Mann-Whitney U test). Presence of erosive joint disease as determined by X-ray; presence of IgM-RF was defined as serum levels ≥ 12.5 U/mL. Statistically significant P-value is marked in bold.

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 60)</th>
<th>Non-responders (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52 (14)</td>
<td>55 (12)</td>
<td>0.34</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>47 (78%)</td>
<td>19 (66%)</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI</td>
<td>25.5 (4.7)</td>
<td>26.8 (4.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (14)</td>
<td>80 (14)</td>
<td>0.06</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.1 (1.0)</td>
<td>5.5 (1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Erosive disease, n (%)</td>
<td>49 (82%)</td>
<td>22 (76%)</td>
<td>0.52</td>
</tr>
<tr>
<td>IgM-RF presence, n (%)</td>
<td>46 (77%)</td>
<td>20 (69%)</td>
<td>0.44</td>
</tr>
<tr>
<td>ACPA presence, n (%)</td>
<td>49 (82%)</td>
<td>21 (72%)</td>
<td>0.32</td>
</tr>
<tr>
<td>ESR (mm/hr) median (IQR)</td>
<td>35 (23)</td>
<td>28 (26)</td>
<td>0.15</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>22 (24)</td>
<td>23 (35)</td>
<td>0.89</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>75 (25-158)</td>
<td>94 (45-165)</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of prior DMARDs</td>
<td>2.1 (1.4)</td>
<td>2.2 (1.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>MTX dosage (mg/week)</td>
<td>19.5 (8.2)</td>
<td>18.1 (8.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Prednison use, n (%)</td>
<td>40 (67%)</td>
<td>22 (76%)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

BMI = body mass index; DAS = disease activity score; RF = rheumatoid factor; ACPA = anti-citrullinated peptide antibodies; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate.
Statistical analysis
Continuous data were described as mean and standard deviation (SD), if normally distributed, and as median and interquartile range (IQR), if not normally distributed. One sample Kolmogorov-Smirnov test was used to test for normal distribution. The unpaired Student’s t-test or, where appropriate, Mann-Whitney U test was used to compare responders and non-responders. The Pearson’s correlation coefficient was used to investigate the relationship between BMI and disease activity. Categorical data were represented as percentages and analyzed using the Chi-square, Fisher’s exact test or linearly by linear association. BMI was divided into three categories (BMI < 20, 20-30 and > 30), and a one-way ANOVA and a post hoc test (Bonferroni) were used to compare patient characteristics in these three groups, as well as clinical response according to the EULAR criteria. The association between ΔDAS28 and BMI at baseline was adjusted for DAS28 at baseline with an ANCOVA. To adjust for DAS28 at baseline logistic regression was used to test if BMI and DAS28 at baseline predict response. Logistic regression was also used to test the influence of BMI, DAS28 and presence of ACPA at baseline on the presence of erosions at baseline. Standard statistical software (SPSS v16.0.2 (SPSS, Chicago, IL) was used for all statistical analyses. A P-value of ≤ 0.05 was considered statistically significant.

RESULTS
Baseline patient characteristics
Eighty-nine RA patients were analyzed. Demographic and clinical features are shown in Table 1. Sixteen weeks after initiation of treatment, the mean DAS28 (SD) decreased from 5.9 (1.1) to 4.1 (1.4) (P < 0.001). Sixty of 89 patients (67%) experienced a decrease in DAS28 (ΔDAS28) ≥1.2 and were termed responders. According to EULAR response criteria 27%, 53%, and 20% of patients, respectively, achieved good, moderate or no response. All baseline patient characteristics were tested for differences between responders (ΔDAS28 ≥1.2) and non-responders (ΔDAS28 <1.2), but only baseline DAS28 was significantly higher in the responder than in the non-responder group (6.1 [1.0] versus 5.5 [1.2], respectively, P = 0.03; Table 1).

BMI and clinical characteristics at baseline
The mean BMI was 26 (SD 5, range 17–42) at baseline and it was not different for responders and non-responders, as determined by ΔDAS28 (P = 0.20; Table 1). Next, we divided BMI into three categories: BMI < 20 (n = 8 [9%]), BMI 20-30 (n = 66 [74%]) and BMI > 30 (n = 15 [17%]) and tested all baseline patient characteristics (Table 2). Presence of erosive disease, ACPA positivity, and DAS28 at baseline were significantly different between the three groups (P = 0.02, P = 0.03 and P = 0.02, respectively). Other characteristics showed no significant differences between the three BMI categories. Interestingly, when BMI, presence of ACPA, and disease duration were entered into a logistic regression model to predict erosive disease, all three parameters were independently related to its presence (P = 0.053, P = 0.003, P = 0.006, respectively; data not shown).

Relationship between BMI and clinical response to infliximab in RA
We found a positive correlation between BMI and DAS28 at baseline (r = 0.34, P = 0.001). Both variables were normally distributed according to the Kolmogorov-Smirnov test (BMI: P = 0.36
and DAS28: \( P = 0.57 \)). Since selecting patients based on DAS28 can influence clinical response, as measured by DAS28, to TNF blockade due to regression to the mean \((19)\), ANCOVA was applied to correct for baseline DAS28. This showed that BMI significantly influenced DAS28 after 16 weeks \(( P = 0.001, B = -0.094; CI -0.149\ldots-0.038)\). This effect was driven by a change in the tender joint count (TJC), swollen joint (SJC) count and visual analogue scale (VAS) domains of the DAS28. In the same way as described above, to adjust for respectively TJC, SJC and VAS at baseline, ANCOVA was used to test the relationship between BMI and the decrease in TJC, SJC and VAS with the following results for TJC: \( P = 0.001, B = -0.482; CI -0.745\ldots-0.218\); SJC: \( P = 0.06, B = -0.196; CI -0.401\ldots0.009\); and VAS: \( P = 0.04, B = -1.080; CI -2.107\ldots-0.052\). There was no statistically significant relationship between BMI at baseline and decrease in CRP levels.

BMI and DAS28 significantly predicted responders \((\Delta\text{DAS28} \geq 1.2)\) to infliximab treatment in a logistic regression model \(( P = 0.03 \text{ and } P = 0.01; \text{Nagelkerke } R^2 = 0.14)\). When BMI was divided into three categories, the percentage of responders \((\Delta\text{DAS28} \geq 1.2)\) significantly decreased in the BMI groups with higher BMI \((84\%, 75\%, \text{ and } 50\%, P = 0.04; \text{Figure 1A})\). Similar statistically significant results were obtained when the BMI at baseline was categorized according to the World Health Organization’s guidelines \((\text{underweight } \leq 18.4:\text{ normal: } 18.5\ldots24.9, \text{ overweight: } 25.0\ldots29.9, \text{ obese } \geq 30 \text{ kg/m}^2; \text{data not shown})\).

Finally, patients were analyzed according to EULAR response criteria. BMI was significantly higher in the non-responder group compared with the good responders \((\text{one-way ANOVA and a post hoc test (Bonferroni; CI } 0.39-7.23, P = 0.03; \text{Figure 1B})})

| Table 2. Baseline patient characteristics for the different BMI groups. Mean values (SD), median (interquartile range [IQR]) or n (%) are shown. Baseline characteristics were compared between three different BMI groups using Chi-square test, one-way ANOVA and Bonferroni test. Statistically significant \( P \)-values are marked in bold. |
|---------------------------------|---------|---------|---------|--------|
| BMI category | \( n = 8 \) | \( n = 66 \) | \( n = 15 \) | \( P \)-value |
| Age | 50 (15) | 57 (11) | 53 (15) | 0.24 |
| Female, n (%) | 6 (75%) | 47 (71%) | 13 (87%) | 0.34 |
| DAS28 | 5.6 (1.2) | 5.9 (1.0) | 6.5 (1.0) | 0.02 |
| Erosive disease, n (%) | 7 (88%) | 56 (85%) | 8 (53%) | 0.02 |
| IgM-RF presence, n (%) | 7 (88%) | 50 (76%) | 9 (60%) | 0.16 |
| ACPA presence, n (%) | 7 (88%) | 55 (83%) | 8 (53%) | 0.03 |
| ESR (mm/hr) (median, IQR) | 31 (21) | 36 (27) | 31 (24) | 0.90 |
| CRP (mg/L) (median, IQR) | 23 (27) | 24 (33) | 17 (15) | 0.55 |
| Disease duration (months) | 75 (21-169) | 112 (49-164) | 54 (31-129) | 0.63 |
| Number of prior DMARDs | 2.0 (1.4) | 2.5 (1.6) | 1.7 (1.1) | 0.56 |
| MTX dosage (mg/week) | 19 (8.1) | 19 (8.4) | 18.8 (8.7) | 0.51 |
| Prednison use, n (%) | 2 (25%) | 22 (33%) | 3 (20%) | 0.54 |

BMI = body mass index; DAS = disease activity score; RF = rheumatoid factor; ACPA = anti-citrullinated peptide antibodies; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate.
Most RA patients showed presence of ACPA in their serum in our study. These antibodies are associated with a more aggressive disease course and it was suggested recently that ACPA-positive patients comprise a specific RA disease subset (20). BMI at baseline was also negatively correlated to D\textsubscript{DAS28} after 16 weeks in the ACPA positive subgroup (data not shown).

**DISCUSSION**

Adipose tissue may have immunomodulating effects in RA although its exact role is at present unclear. Hence, we investigated prospectively whether BMI is associated with response to infliximab in RA patients. BMI was positively correlated with baseline D\textsubscript{DAS28}, indicating a more active disease in our heavier patients. Of importance, a higher BMI resulted in a decreased clinical response (as determined by both D\textsubscript{DAS28} and EULAR criteria) to infliximab after 16 weeks of treatment, even after adjustment for baseline D\textsubscript{DAS28} or ACPA status, in spite of the fact that this drug is dosed per kilogram body weight. To the best of our knowledge, this is the first published study evaluating the effect of BMI on response to TNF blockade in any immune-mediated inflammatory disease, for which RA is a prototype.

These findings do not seem due to pharmacological reasons. It is known that the response to infliximab is related to infliximab concentrations in serum\textsuperscript{21} and that the volume of distribution of infliximab corresponds to the intravascular space\textsuperscript{22}. As the dose of infliximab is adjusted for body weight and the intravascular space is relatively small in the more obese, one might expect serum infliximab concentrations to be higher in more obese patients, although data are presently lacking in the published literature. However, this study clearly indicated that despite higher doses of infliximab used in patients with increased BMI, the clinical response was diminished. Furthermore, it is conceivable that high levels of disease activity, which are associated with a better response to TNF blockade\textsuperscript{14}, could lead to rheumatoid cachexia and
a reduced BMI, but in our cohort we observed the opposite. Therefore, adipose tissue itself might play a role in creating a more therapy-resistant state.

Adipose tissue is not only a source of pro-inflammatory cytokines, like TNF and IL-6, but also of specific adipocytokines. Serum levels of, for example, leptin, resistin, adiponectin, and visfatin are all increased in RA patients compared with healthy controls. Several of these mediators may be associated with clinical signs and symptoms of RA and the induction of resistance to TNF blockade, but their role in the process of joint destruction may be more complex. Our results showed that a high BMI was associated with less erosions at baseline and, as earlier studies have shown, obesity might have a protective effect on radiological joint damage over time. More specifically, adiponectin concentrations were found to be negatively correlated with joint damage in RA patients. Thus, adipose-tissue derived mediators may be one of the long sought after missing links in the uncoupled occurrence of synovial inflammation and joint destruction that may be observed in chronic arthritis. It should be noted, however, that the effect of BMI on DAS28 after 16 weeks was driven by a change in TJC, SJC, and VAS rather than CRP levels, which could argue a bit against a mechanism involving adipose tissue-derived mediators of inflammation.

This study has some limitations. First the number of 89 patients is relatively small. Second, we did not have access to an independent cohort to confirm our findings. However, recently the Italian Gisea registry study (collecting data of all RA and spondylarthropathy patients treated with biologicals in 14 centers in Italy) also found that obesity is associated with lower response to various biologicals, confirming our findings. The validity of our findings is also supported by the observation that when BMI was divided into three categories, the percentage of responders significantly decreased in the groups with higher BMI (respectively, 84%, 75%, and 50%). Third, data on total fat mass compared with regional fat mass, as well as levels of various adipocytokines, were not available, but the current study does provide a rationale for more detailed studies on the role of adipose tissue in conditions like RA, psoriasis and Crohn’s disease in relation to the response to anti-TNF therapy. Fourth, response was measured after 16 weeks and therefore we cannot exclude the possibility that RA patients with higher BMI could respond later compared to leaner RA patients. We chose to select a fixed endpoint at 16 weeks to ascertain assessment of the primary response to infliximab treatment, as the secondary response defined at later time points may be influenced by totally unrelated mechanisms, including the development of human anti-chimeric antibodies against infliximab.

In conclusion, RA patients with a high BMI exhibited a diminished clinical response to infliximab treatment, despite drug dosing by body weight, suggesting adipose tissue could play a role in RA pathophysiology.

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SUPPLEMENTAL FIGURES

Supplemental figure 1. Clinical response and body mass index (BMI) in rheumatoid arthritis (RA) patients after 16 weeks of treatment with infliximab (3 mg/kg i.v., administered at baseline, week 2, 6 and 14) Clinical responders (defined as decrease in DAS28 ≥1.2) in BMI groups at baseline in all RA patients. BMI is dichotomized according to world health organization BMI categorization (underweight ≤ 18.4 normal: 18.5–24.9, overweight: 25.0–29.9, obese ≥30 kg/m2). (* means P ≤ 0.05)