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## HIGH BODY MASS INDEX AND REDUCTION OF RESPONSE TO RITUXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS

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**ABSTRACT:** Adipose tissue has immunomodulating effects in rheumatoid arthritis (RA). Previous studies suggested that obesity could negatively affect the response to anti-TNF- $\alpha$  agents. We aimed to determine whether body mass index (BMI) is involved in the response to the anti-CD20 "Rituximab" in RA. In 100 patients with active RA, the BMI was categorized into two groups ( $<25$  kg/m<sup>2</sup> and  $\geq 25$  kg/m<sup>2</sup>) and calculated before initiation of rituximab treatment. Changes from baseline in Disease Activity Score in 28 joints (DAS28); Health Assessment Questionnaire (HAQ) disability index; C-reactive protein levels (CRP); erythrocyte sedimentation rate levels (ESR); tender and swollen joint count (TJC, SJC); pain and global on a visual analog scale (VAS) were analyzed within 12 weeks. The primary outcome was decreased in DAS28  $\geq 1.2$ , while secondary outcomes were the European League against Rheumatism (EULAR) response criteria. Radiographical erosive status and adipokine levels of pigment epithelium-derived factor (PEDF) and chemerin were also evaluated. As a result, the mean  $\pm$  SD of BMI for all patients was  $27 \pm 4.6$  kg/m<sup>2</sup>. The BMI correlated positively with the DAS28 at baseline ( $r=0.42$ ,  $P<0.05$ ). Alterations in the disease activity components were associated with a change in the HAQ, TJC, and VAS of pain and global. According to the EULAR response criteria, BMI values were significantly higher in the non-responder, compared with the good responder group ( $P<0.05$ ). In the heavier RA patients, erosive status was less, while adipokine levels of PEDF and chemerin were more. In conclusion, RA patients with a high BMI responded less well to rituximab.

**INTRODUCTION:** Excess adipose tissue in obese individuals may have immunomodulating properties, through the release of adipocytokines, and pharmacokinetic consequences<sup>1, 2</sup>. Obesity might be a risk factor for rheumatoid arthritis (RA) developing from undifferentiated arthritis and is associated with decreased radiographic evidence of disease progression in RA<sup>3, 4</sup>.

Many reports showed a negative association between body mass index (BMI) and response to anti-TNF- $\alpha$  therapies in RA<sup>5-7</sup>, psoriatic arthritis<sup>8, 9</sup>, and ankylosing spondylitis<sup>10, 11</sup>, which suggests that fat mass may affect the response to biologic agents. Here, we investigated whether BMI could affect the response to the anti-CD20 "rituximab" among RA patients.

**Patients and Methods:** One-hundred patients gave written informed consent under the supervision of specialist physicians in three Hospitals of Baghdad-Iraq, department of Rheumatology, during February to July 2016. The study was approved by the Scientific and Ethical Committee of the Academic Research, College of Pharmacy/

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University of AL-Mustansiryiah. Those patients suffered from active rheumatoid arthritis, according to the American College of Rheumatology criteria<sup>12</sup>. The baseline demographic and clinical features of the patients are summarized in **Table 1**. Patients were selected for the present analysis based on the availability of BMI data, serum samples obtained at baseline, and standardized clinical follow-up data on the response to rituximab treatment. Rituximab was given IV (1g) on days 1 and 15, with pre-medication by cetirizine and IV

methylprednisolone (100 mg) according to recommendations<sup>13</sup>.

All study patients were taking stable dosages of methotrexate (5-30 mg/week) and had active disease, as defined by a Disease Activity Score in 28 joints (DAS28)  $\geq 3.2$ . Use of oral corticosteroids ( $\leq 10$  mg/day) and NSAIDs was allowed if the dose had not been changed within one month prior to baseline. Patients who had received an intra-articular injection of steroids within the previous month were excluded.

**TABLE 1: BASELINE CHARACTERISTICS OF RHEUMATOID ARTHRITIS PATIENTS TREATED WITH 12 WEEKS OF RITUXIMAB, ACCORDING TO REMISSION STATUS.**

Baseline characteristics	Remission N=67 (67%)	No remission N=33 (33%)
Age (mean $\pm$ SD), year	54 $\pm$ 13	53 $\pm$ 16
Female gender, no (%)	50 (75)	25 (76)
Weight (mean $\pm$ SD), kg	72 $\pm$ 11	83 $\pm$ 15
BMI (mean $\pm$ SD), kg/m <sup>2</sup>	25.1 $\pm$ 3.8	29.3 $\pm$ 5.6 *
Disease duration (mean $\pm$ SD), year	12.2 $\pm$ 8.1	11.9 $\pm$ 7.6
Erosive status, no. (%)	46 (69)	17 (52)
IgM-RF positive, no. (%)	52 (78)	20 (61)
ACPA positive, no. (%)	54 (81)	24 (73)
DAS28 (mean $\pm$ SD)	4.0 $\pm$ 1.3	4.7 $\pm$ 1.4 *
HAQ score (mean $\pm$ SD)	1.4 $\pm$ 0.6	1.3 $\pm$ 0.5
CRP (mean $\pm$ SD), (mg/L)	40 $\pm$ 3.8	35 $\pm$ 4.2
ESR (mean $\pm$ SD), (mm/hr)	39 $\pm$ 16.5	41 $\pm$ 14.3
TJC (68 joints) (mean $\pm$ SD)	13 $\pm$ 7.8	15 $\pm$ 6.7
SJC (66 joints) (mean $\pm$ SD)	16 $\pm$ 8.5	15 $\pm$ 9.3
VAS pain (mean $\pm$ SD)	53 $\pm$ 11.6	55 $\pm$ 12.1
VAS global (mean $\pm$ SD)	54 $\pm$ 12.6	53 $\pm$ 11.2
Current oral steroids, no. (%)	45 (67)	23 (70)
Current oral steroids dose, mg/day	9.7 $\pm$ 0.3	8.9 $\pm$ 0.6
MTX dose (mean $\pm$ SD), mg/wk	16.5 $\pm$ 8.7	16.6 $\pm$ 9.8
Previous DMARDs (mean $\pm$ SD)	2.6 $\pm$ 1.9	2.4 $\pm$ 1.7
Previous anti-TNF- $\alpha$ , no. (%)	43 (64)	24 (73)
Inefficient anti-TNF- $\alpha$ , no. (%)	27 (40)	14 (42)

Remitters were patients who had a decrease in the Disease Activity Score in 28 joints (DAS28) of  $\geq 1.2$  after 12 weeks of treatment. BMI = body mass index; Serum IgM rheumatoid factor (IgM-RF) titers  $\geq 12.5$  units/ml were considered positive. ACPA = anti-citrullinated protein antibody; HAQ = Health Assessment Questionnaire Disability Index score; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; TJC = Tender joint count; SJC = Swollen joint count; VAS = visual analog scale; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; TNF- $\alpha$  = tumor necrosis factor-alpha. Data expressed by mean  $\pm$  SD or no. (%). \* consider  $P \leq 0.05$ .

Remission status was defined as the change in the DAS28 after 12 weeks of therapy, as compared with baseline. Rheumatoid arthritis patients with the change of DAS28 values  $\geq 1.2$  was considered as a primary outcome, representing a clinically significant improvement and defined as remitters<sup>14</sup>. The response was also determined according to the European League against Rheumatism (EULAR) response criteria<sup>15</sup>, which considered as a secondary outcome and divided into 3 categories: good response, moderate response, and no response

(**Table 2**). As a supplementary outcome, Health Assessment Questionnaire (HAQ) Disability Index score; C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); tender joint count (TJC); swollen joint count (SJC); and visual analog scale (VAS) were also evaluated. Clinical response was evaluated within 12 weeks since a significant improvement is expected to occur within three months, after which alternative treatment should be considered<sup>16</sup>.

**TABLE 2: EULAR RESPONSE CRITERIA**

DAS28	Improvement in DAS28		
	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	Good response	Moderate response	No response
> 3.2 and ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

DAS28 = Disease Activity Score in 28 joints.

Considering laboratory tests at baseline, the presence of IgM-RF (abcam<sup>®</sup> kit) and ACPAs (Biocompare<sup>®</sup> anti-CCP kit) were measured by ELISA technique; CRP (Diagnostic Automation Incorporation<sup>®</sup> kit) by latex test method; and ESR (Sedi-Rate<sup>®</sup> kit) by Westergren Starter method. Serum levels of the two adipokines, pigment epithelium-derived factor (PEDF) and chemerin, were also assessed at a baseline level, using ELISA kit technique (provided by Biovendor<sup>®</sup> and Abcam<sup>®</sup> company, respectively).

The presence of erosive joint disease, as determined radiographically, was also assessed at baseline. Radiographs of the hands and feet were taken at screening using the Genant modified sharp scoring method and other scores to assess erosion status<sup>17</sup>. Radiographic evaluations were performed by two independent readers who were blinded to the study treatment. Height and body weight were measured at baseline using a fixed scale with a stadiometer (Tanita TBF-215, Tokyo, Japan) and the BMI was calculated as the weight (kg) divided by the height (m<sup>2</sup>). The BMI was categorized into two groups, <25 kg/m<sup>2</sup> and ≥ 25 kg/m<sup>2</sup>.

**Statistical analysis:** Continuous variables were expressed as mean ± SD, while categorical variables were expressed as frequencies and percentages. Student's unpaired t-test and Mann-Whitney U-test were used to compare remitters and non-remitters. Pearson's correlation coefficient was used to detect the relationship between BMI and disease activity. Categorical variables differences were analyzed by chi-square, Fisher's exact test or analyzed linearly by linear association. One-way analysis of variance (ANOVA) test was used to compare patient characteristics in the two BMI groups, also to compare the three categories of clinical response according to the EULAR response criteria.

The association between the changes in DAS28 and BMI at baseline was adjusted for the DAS28 values

at baseline with the use of an analysis of covariance (ANCOVA). To adjust for the DAS28 at baseline, stepwise logistic regression model was used to test whether the BMI and the DAS28 at baseline predicted treatment response. Logistic regression model was also used to test the influence of BMI, disease duration, and positivity of ACPAs (anti-CCP) on the erosive status at baseline. All of the analyses were performed using SAS (version 9.2) and *P*-value ≤ 0.05 was considered statistically significant.

## RESULTS:

**Baseline characteristics according to remission status:** Demographic and clinical features of one-hundred evaluated patients are shown in the **Table 1**. Twelve weeks after initiation of treatment, the mean ± SD of DAS28 for all patients decreased from 4.3 ± 1.2 to 3.0 ± 1.4 (*P*<0.05). Of the one-hundred RA patients, 67(67%) experienced a decrease in the DAS28 of ≥1.2 and are referred to as "remitters" while just 33 (33%) have a change in DAS28 of <1.2 and are referred to as "non-remitters". All baseline characteristics of the studied patients were tested to compare between both groups, but only the baseline DAS28 and BMI were significantly lower in the remitter than non-remitter group (4.0±1.3 vs. 4.7±1.4; and 25.1±3.8 kg/m<sup>2</sup> vs. 29.3±5.6 kg/m<sup>2</sup>, respectively: *P*<0.05).

**Baseline characteristics according to BMI categories:** The mean ± SD of BMI for all patients was 27±4.6 kg/m<sup>2</sup> at baseline, and it was differ significantly between remitters and non-remitters (*P*<0.05) (**Table 1**). Meanwhile, BMI was divided into two categories and all baseline characteristics for these categories was tested (**Table 3**). Of the one-hundred RA patients, 63(63%) had a BMI <25 kg/m<sup>2</sup> and 37 (37%) had a BMI ≥25 kg/m<sup>2</sup>. Values of BMI, DAS28, and frequencies of erosive features at baseline was differ significantly between the two BMI categories (23.1±2.8; 4.1±1.2; 75% for BMI <25 kg/m<sup>2</sup> vs. 30.1±5.8; 4.6±1.7; 49% for BMI ≥25 kg/m<sup>2</sup>, respectively, *P*<0.05).

Other characteristics showed no significant differences between the two BMI categories ( $P>0.05$ ). Interestingly, when the baseline BMI, disease duration, and positivity of ACPA (anti-

CCP) were entered into a logistic regression model to predict erosive status, all of these parameters were independently related to its presence ( $P<0.05$ ) (data not shown).

**TABLE 3: BASELINE CHARACTERISTICS OF RHEUMATOID ARTHRITIS PATIENTS TREATED WITH 12 WEEKS OF RITUXIMAB, ACCORDING TO BMI CATEGORIES.**

Baseline Characteristics	BMI < 25 mg/m <sup>2</sup> N=63 (63%)	BMI ≥ 25mg/m <sup>2</sup> N=37 (37%)
Age (mean ± SD), year	53±14	56±13
Female gender, no (%)	48 (76)	26 (70)
Weight (mean ± SD), kg	70±13	86±14
BMI (mean ± SD), kg/m <sup>2</sup>	23.1±2.8	30.1±5.8 *
Disease duration (mean ± SD),year	11.3±6.1	13.7±6.6
Erosive status, no. (%)	47 (75)	18 (49) *
IgM-RF positive, no. (%)	52 (83)	28 (76)
ACPA positive, no. (%)	50 (79)	27 (73)
DAS28 (mean ± SD)	4.1±1.2	4.6±1.7*
HAQ score (mean ± SD)	1.5±0.7	1.4±0.6
CRP (mean ± SD), (mg/L)	39±3.5	34±3.2
ESR (mean ± SD), (mm/hr)	41±15.6	39±17.4
TJC (68 joints) (mean ± SD)	15±5.8	14±7.7
SJC (66 joints) (mean ± SD)	15±8.3	16±8.3
VAS pain (mean ± SD)	52±10.6	57±11.1
VAS global (mean ± SD)	53±12.7	58±13.2
Current oral steroids, no. (%)	42 (67)	25 (68)
Current oral steroids dose, mg/day	9.2±0.8	9.7±0.5
MTX dose (mean ± SD), mg/wk	17.5±5.3	15.8±9.6
Previous DMARDs (mean ± SD)	2.1±1.4	2.5±1.3
Previous anti-TNF-α, no. (%)	38 (60)	23 (62)
Inefficient anti-TNF-α, no. (%)	26 (41)	16 (43)

BMI = body mass index; Serum IgM rheumatoid factor (IgM-RF) titers  $\geq 12.5$  units/ml were considered positive. ACPA = anti-citrullinated protein antibody; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire Disability Index score; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; TJC = Tender joint count; SJC = Swollen joint count; VAS = visual analog scale; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; TNF-α = tumor necrosis factor-alpha. Data expressed by mean ± SD or no. (%). \* consider  $P \leq 0.05$ .

**BMI and clinical response to rituximab:** A positive correlation was found between BMI and DAS28 values at baseline ( $r = 0.42$ ,  $P < 0.05$ ). Since the selection of the studied patients according to DAS28 values can influence the clinical response to rituximab due to regression to the mean, because the clinical response itself based on the change in the DAS28 values, ANCOVA was applied to adjust for the baseline DAS28. This analysis showed that BMI significantly influenced the change in DAS28 after 12 weeks of treatment ( $P < 0.05$ ).

The alterations in the disease activity components were associated with a change in the HAQ disability index; TJC; VAS pain and global rather than a change in the SJC (**Fig. 1**). To adjust for these parameters at baseline, ANCOVA was used, as described above, to test the relationship between

BMI and the decrease in these scores. This analysis showed that BMI significantly influenced the change in the above scores at the end of the study ( $P < 0.05$ ). However, no statistically significant relationship was found between BMI and the decrease in the levels of laboratory parameters of inflammation (CRP and ESR) after completion of 12 weeks ( $P > 0.05$ ).

The BMI and DAS28 significantly predicted the remitters to rituximab treatment (change of DAS28  $\geq 1.2$ ), as demonstrated in a logistic regression model ( $P < 0.05$ ) (data not shown). When BMI was divided into two categories, the percentage of remitters significantly decreased in the group with a higher BMI (67%) compared with those having a lower BMI (89%) ( $P < 0.05$ ) (**Fig. 2A**). Moreover, when patients were analyzed according to the EULAR response criteria, the BMI values were

significantly higher in the non-responder, as compared with the good responder group ( $P < 0.05$ ) (Fig. 2B). According to these criteria, 25%, 57%,

and 18% of patients achieved a good response, moderate response, and no response, respectively.

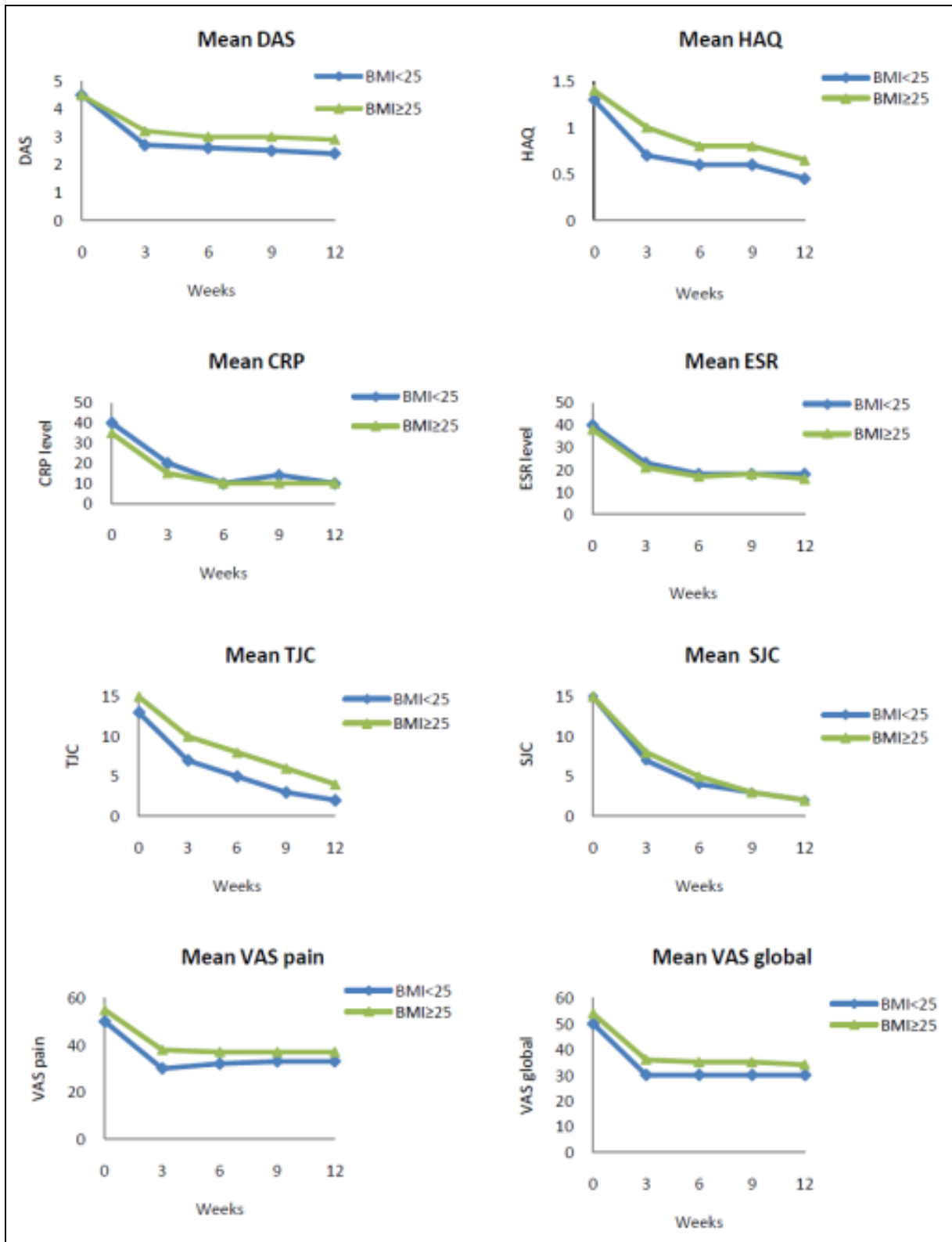
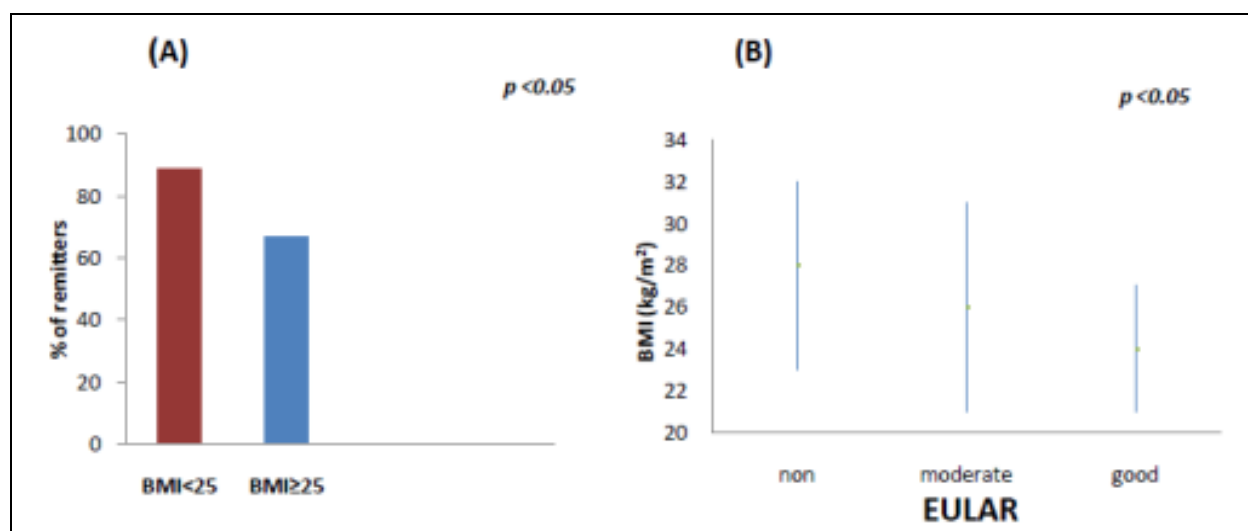


FIG. 1: DISEASE ACTIVITY COMPONENTS DURING 12 WEEKS OF TREATMENT WITH RITUXIMAB, BASED ON BODY MASS INDEX (BMI) CATEGORIES. DAS = DISEASE ACTIVITY SCORE; HAQ = HEALTH ASSESSMENT QUESTIONNAIRE; CRP = C-REACTIVE PROTEIN; ESR = ERYTHROCYTE SEDIMENTATION RATE; TJC = TENDER JOINT COUNT; SJC = SWOLLEN JOINT COUNT; VAS = VISUAL ANALOG SCALE.



**FIG. 2: CLINICAL RESPONSE AND BODY MASS INDEX (BMI) IN RHEUMATOID ARTHRITIS (RA) PATIENTS AFTER 12 WEEKS OF TREATMENT WITH RITUXIMAB. (A): PERCENTAGES OF PATIENTS DEFINED AS RESPONDERS (REMITTERS) BASED ON THE DISEASE ACTIVITY SCORE IN 28 JOINTS (DAS28), ACCORDING TO BMI GROUP AT BASELINE. REMITTERS (N=67) WERE THOSE WHO EXPERIENCED A DECREASE OF  $\geq 1.2$  IN THE DAS28. (B): BMI VALUES AT BASELINE ACCORDING TO THE EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) RESPONSE GROUP AT 12 WEEKS. VALUES EXPRESSED AS MEAN  $\pm$  SD.**

Radiographic evaluation for the observed cases showed a trend toward less progression of joint damage in the heavier patients (Table 4). At baseline, the total joint space narrowing score was significantly higher in patients with BMI < 25 mg/m<sup>2</sup> compared with those having BMI  $\geq 25$  mg/m<sup>2</sup> ( $3.7 \pm 1.4$  vs.  $2.3 \pm 1.2$ , respectively,  $P < 0.05$ ). In patients having BMI  $\geq 25$  mg/m<sup>2</sup>, the baseline

total Genant-modified Sharp score and total erosion score were less than those with BMI < 25 mg/m<sup>2</sup>, this difference was not statistically significant between BMI groups ( $P > 0.05$ ), although it numerically favored those with less BMI. Moreover, the frequency of erosive disease was significantly less in the heavier patients ( $P < 0.05$ ) (Table 3).

**TABLE 4: EROSION STATUS AT BASELINE ACCORDING TO BMI**

Radiographic Scores	BMI < 25 mg/m <sup>2</sup>	BMI $\geq 25$ mg/m <sup>2</sup>
Total Genant-modified Sharp score	$2.1 \pm 1.7$	$1.6 \pm 1.3$
Total joint space narrowing score	$3.7 \pm 1.4$	$2.3 \pm 1.2$ *
Total erosion score	$2.5 \pm 1.9$	$1.9 \pm 1.5$

Values expressed as mean  $\pm$  SD. BMI = Body Mass Index. \* consider  $P \leq 0.05$ .

Regarding baseline serum levels of the two adipokines, pigment epithelium-derived factor (PEDF) and chemerin were significantly higher in

RA patients with BMI  $\geq 25$  mg/m<sup>2</sup>, compared with those having BMI < 25 mg/m<sup>2</sup> ( $P < 0.05$ ) (Table 5).

**TABLE 5: LEVELS OF ADIPOKINES AT BASELINE ACCORDING TO BMI.**

Adipokines	BMI < 25 mg/m <sup>2</sup>	BMI $\geq 25$ mg/m <sup>2</sup>
PEDF (ng/ml)	$6.1 \pm 2.3$	$12.4 \pm 3.6$ *
Chemerin (ng/ml)	$13.5 \pm 3.4$	$19.6 \pm 4.1$ *

Values expressed as mean  $\pm$  SD. BMI = Body Mass Index. PEDF = pigment epithelium-derived factor.

\* consider  $P \leq 0.05$ .

**DISCUSSION:** Although its exact role is presently unclear, adipose tissue may have immunomodulating effects in RA. Hence, we prospectively investigated whether BMI is associated with response to rituximab in RA patients. This study focused on patients who were

taking anti-TNF- $\alpha$  drugs due to persistent unresponsiveness to MTX and who did not change their standard therapy. Besides being patients with longstanding RA, the disease was already persistent, stable, and active.

The baseline BMI showed a positive correlation with the baseline DAS28, indicating a high active disease in our heavier patients. Of importance, a higher BMI resulted in a decreased clinical response to rituximab (as determined by DAS28 and EULAR criteria) after 12 weeks of treatment. It was noted that female gender was approach between both BMI groups, and the DAS28 scores among females increased with increasing BMI<sup>18</sup>.

Most RA patients in this study had ACPAs (anti-CCP) and IgM-RF in their serum. These antibodies are associated with a more aggressive disease course, and it was suggested that ACPA-positive patients represent a specific RA disease subset<sup>19</sup>. The BMI at baseline was also negatively correlated with the change in DAS28 after 12 weeks in the ACPA-positive subgroup. Anti-CCP and RF positivity were found to be associated with better response to rituximab<sup>20, 21</sup>. Moreover, the published data on the RA population suggesting that high anti-CCP titer could be associated with response to rituximab<sup>22</sup>.

Adipose tissue is a source not only of proinflammatory cytokines, like TNF- $\alpha$  or IL-6; but also of specific adipocytokines<sup>1</sup>. Serum levels of leptin, resistin, adiponectin, and visfatin are all increased in RA patients, compared with healthy controls<sup>23</sup>. Several hypotheses could explain the role of excess adipose tissue in RA response to anti-TNF- $\alpha$  agents. Adipokines secreted in adipose tissue could increase the level of pro-inflammatory cytokines, thus leading to an inflammatory basal state. To date, the influence of anti-TNF- $\alpha$  agents on adipokines levels remains unclear<sup>24</sup>. Pharmacokinetics of infliximab, for example, might be altered by an excess of adipose tissue. It could be hypothesized that the volume of distribution of a non-lipophilic drug, such as infliximab, could be decreased by excess adipose tissue<sup>2</sup>. This could explain the restrictive negative effect of BMI on the infliximab response, a drug that given IV in a dose based on body weight, as compared with other anti-TNF- $\alpha$  agents administered by SC route (like etanercept and adalimumab)<sup>6</sup>. In a certain study and after 16 weeks of treatment with infliximab, 89 patients observed a highly significant negative association between BMI and the absolute decrease in DAS28<sup>5</sup>. From a clinical point of view, this appears to be extremely important because the

persistence of inflammation already represents a high risk of cardiovascular disease, and RA is considered at the same risk level as type 2 diabetes mellitus<sup>25, 26</sup>.

Indeed, increased adipose tissue is a source of inflammation that leads to insulin resistance<sup>27</sup>. Hence, insulin resistance could be considered as an important marker of excess adipose tissue-related inflammation. Of interest, anti-TNF- $\alpha$  agents were ineffective in reducing insulin resistance in obese RA patients<sup>28</sup>. In contrast, rituximab therapy was successfully used for treating patients with type B syndrome of severe insulin resistance<sup>29</sup>. Therefore, in contrast to anti-TNF- $\alpha$  agents, rituximab could decrease inflammation in patients with increased adipose tissue. However, in this study, the proportion of RA patients receiving rituximab who previously received anti-TNF- $\alpha$  therapy was approach among both BMI categories.

It should be noted that the effect of BMI on the change of DAS28 after 12 weeks was driven by a change in the HAQ, TJC and VAS domains of the DAS28 rather than SJC and laboratory parameters of inflammation (CRP and ESR), which could represent an evidence against a mechanism involving adipose tissue-derived mediators of inflammation. Higher pain scores and worse global health were also reported in patients with a high BMI in a large cohort study<sup>30</sup>. In that study, patients with a BMI  $\geq 30$  kg/m<sup>2</sup> also had a higher CRP and ESR level at follow-up. We found no association between BMI and the parameters of inflammation or joint swelling.

Regarding the difficult to clinically assess SJC in an overweight patient compared to normal weight one, it could be hypothesized that SJC was underestimated in this group of patients. The higher TJC in patients with a high BMI might still reflect more local inflammation. It's previously reported that local joint tenderness is a predictor of local joint damage after one year, independent of swelling<sup>31</sup>. This, in fact, supports the practice of using a composite score such as "DAS" as a treatment target, not merely joint swelling.

Certain study reports that obesity could be associated with fibromyalgia, suggesting that TJC could be enhanced in these obese patients<sup>32</sup>.

We did not do routine assessments of fibromyalgia features, but we cannot exclude that a fibromyalgia component was present in part of these patients.

Self-reported pain, especially musculoskeletal pain, is higher in patients with a high BMI, in particular with a BMI  $\geq 30$  kg/m<sup>2</sup>, and they are more likely to report pain in multiple locations<sup>33, 34</sup>. The mechanism of the relationship between obesity and pain is unclear, but it is suggested that disturbances in neurotransmitters and hormones might be, at least partially, responsible<sup>35</sup>. This relation between BMI and pain may also influence the association between high BMI and functional disability, which was found in this study. Pain and body size itself may both interfere with the daily activities that represented by HAQ disability index score<sup>36</sup>.

Our results showed that a high BMI was associated with fewer erosions at baseline, particularly for the total joint space narrowing score and, as earlier studies have shown, obesity might have a protective effect on radiologic joint damage over time<sup>4, 37</sup>. More specifically, adiponectin and leptin concentrations, which elevated in obese patients, have been found to be negatively correlated with joint damage in RA patients<sup>23, 38</sup>.

The adipokine family is continuously growing and among the emerging adipokines, pigment epithelium-derived factor (PEDF) and chemerin seem to be key players in linking obesity and inflammation in rheumatic diseases, as with the established role of the old adipokines (leptin, resistin, adiponectin, and visfatin)<sup>23</sup>.

To support the possible role of PEDF as a player in the inflammatory burden of RA, one study observed that the circulating PEDF levels, evaluated in a cohort of patients with early RA at the time of diagnosis, were higher in obese and overweight than in normal-weight subjects and correlated with systemic inflammation<sup>39</sup>. Previous studies found that chemerin levels directly correlated with disease activity in RA<sup>40, 41</sup>. However, it is not yet completely clear whether the circulating levels of chemerin in patients with RA are more associated with systemic inflammation or adipose tissues itself, but its role is confirmed as a biomarker of disease activity. Our results consisted with these findings, where the baseline serum

levels of the two adipokines, pigment epithelium-derived factor (PEDF) and chemerin, were significantly higher with the heavier weight-more active RA patients. In this regard, these adipokines may provide a metabolic link between obesity and RA disease activity or other autoimmune diseases and as such, they could be possible biomarkers of the effect of weight loss and the decreased fat tissue in chronic inflammatory diseases.

This study has some limitations. First, the number of patients studied is relatively small. Second, we did not have access to an independent cohort in which to confirm our findings. Third, data on total fat mass as compared with regional fat mass were not available. Fourth, the response was measured after 12 weeks of treatment, therefore we cannot exclude the possibility that RA patients with a higher BMI could respond later and approach to RA patients who were leaner. We chose a fixed endpoint of 12 weeks to assess the primary response to rituximab treatment, since the secondary response defined at a later time may be influenced by entirely unrelated mechanisms, including the development of human anti-chimeric antibodies against rituximab<sup>42</sup>. Finally, the design of this study did not allow for investigating the pharmacokinetic consequences of high BMI.

Yet, there are no algorithms for choosing among the biologic agents as a rescue therapy in obese patients with RA. The findings appear relevant when one considers the need of a personalized therapy<sup>43</sup>. Moreover, the results indicate importance in terms of pharmacoeconomics, which means achieving the best possible results by making the right choice at any phase of the disease in a patient with a poor response to MTX. Additional research, including advanced imaging techniques and biomarker studies, may further elucidate the relation between BMI and response to RA treatment, thus helping us to decide how we can best treat our individual patients.

**CONCLUSION:** A high DAS28 score in the therapeutic protocol certainly play the most relevant role in determining the chance of RA remission, and patients with a high BMI exhibited a diminished clinical response to rituximab treatment, suggesting that adipose tissue could play a role in the pathophysiology of this disorder.



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