

The association of body mass index with disease activity and clinical response to combination therapy in patients with rheumatoid arthritis

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Background: The role of obesity in clinical course of rheumatoid arthritis (RA) is not clear. We investigated the association of obesity and adiposity with disease activity and clinical response to combination therapy in RA patients. **Materials and Methods:** Active RA patients with the disease activity score using 28 joint counts (DAS28) > 2.6 were studied. Height, weight, and waist and hip circumferences were measured and body mass index (BMI) and waist to hip ratio were calculated. Patients were treated with methotrexate (7.5 to 10 mg/week) plus hydroxychloroquine (200 to 400 mg/day) and prednisolone (2.5 to 10 mg/day) and were followed by DAS28 for up to 24 weeks. **Results:** One hundred and six patients were studied; age = 48.5 ± 13.8 years, 87.7% female, disease duration = 4.4 years [SE = 0.48]. DAS28 was decreased from 4.5 ± 1.6 to 2.9 ± 1.4 ($P < 0.001$) after 24 weeks of treatment. Only in patients with disease duration of ≤2 years, BMI ($r = -0.415$, $P = 0.005$) and waist circumference ($r = -0.296$, $P = 0.05$) were correlated with baseline DAS28. Although BMI ($r = -0.337$, $P = 0.025$) and waist circumference ($r = -0.315$, $P = 0.038$) were correlated with change in DAS28 after therapy, these correlations were disappeared after controlling for baseline DAS28. **Conclusion:** Obesity and adiposity are associated with less severe disease activity in early stage of RA, but are not associated with response to combination therapy with methotrexate plus hydroxychloroquine in RA patients.

Key words: Adiposity, adipose tissue, hydroxychloroquine, methotrexate, obesity, rheumatoid arthritis, treatment outcome

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INTRODUCTION

Body weight change in patients with rheumatoid arthritis (RA) is a complex issue. On one hand, active disease could lead to weight loss and frank wasting, termed rheumatoid cachexia, which correlates with the intensity of systemic inflammation.^[1] On the other hand, some studies showed that a higher body mass index (BMI) is associated with less severe radiographic joint damage in the early phases of the disease.^[2] Even, some evidence showed that all-cause mortality and cardiovascular-related mortality rates decrease with increasing BMI in RA patients.^[3,4] The subject becomes more complex when considering the adipose tissue as an active site that, by releasing adipocytokines, has some immunological effects.^[5] Therefore, it seems to be a bi-directional relationship between body weight change and disease activity in patients with RA, which is not only affected by biological factors but also by patients' behaviors and life style.^[6]

The association of BMI and the amount of body fat with clinical course of RA is still a matter of debate, and

clinical applications of current data are not clear. Some studies with long follow-up periods have showed that obesity is associated with worse outcomes,^[7] while others have found lower BMI to be associated with decreased survival, and higher BMI as being protective.^[8] Also, some data are available on the association between BMI and treatment response in RA patients. In this regard, recent studies reported that a higher BMI is associated with less well response to antitumor necrosis factor alpha (anti-TNF α) agents.^[9,10] Considering the controversial and complex results of the previous studies and lack of data, the primary aim of this prospective study was to determine whether body fat composition affects response to combination therapy with disease-modifying antirheumatic drugs (DMARDs) including methotrexate plus hydroxychloroquine in RA patients. Moreover, RA patients may encounter a decrease in muscle mass that can mask the increase in fat mass and result in having a normal BMI. Therefore, BMI cannot distinguish between the tissues that comprise it and may not accurately reflect the body fat content. Hence, the secondary aim of this study was to evaluate, in addition to BMI, the association of other anthropometric measurements including

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waist and hip circumferences and waist to hip ratio with treatment response, because they can provide more accurate information about the body fat distribution.^[11]

MATERIALS AND METHODS

Patients and settings

This observational cohort study was conducted on patients with RA (16 to 80 year old) referred to the rheumatology clinic of a University Hospital in Isfahan (central Iran) in 2012. Consecutive patients who met the American College of Rheumatology (ACR) criteria for the classification of RA^[12] and had active disease based on the disease activity score using 28 joint counts (DAS28) >2.6 were included.^[13] Those with previous toxicity to combination therapy with methotrexate plus hydroxychloroquine, and those with significant change of BMI ($\geq 10\%$) in the preceding three months were not included. Also, we excluded patients whose treatment contained DMARDs or drugs other than methotrexate plus hydroxychloroquine (e.g. sulfasalazine). Considering type-I error = 0.05, study power = 0.8, and expecting correlation between BMI and Δ DAS28 as at least 0.3,^[9] the sample size was calculated as 106 cases. The ethics committee of the Isfahan University of Medical Sciences approved the study and informed consent was obtained from all patients.

Assessments

An internist interviewed with all patients and gathered demographic data (age, gender) and clinical data (disease duration, previous therapies) from patients' history and documents. Height, weight, and waist and hip circumferences were measured by an educated nurse. Body mass index (calculated as weight in kilograms divided by the square of height in meters) was categorized into underweight (<18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), and obese (≥ 30 kg/m²).^[14] Patients were examined by a single rheumatologist who evaluated the number of swollen/tender joints, patient's global activity (general health) on a visual analog scale (VAS, 0 to 100), and disease functional class based on the American College of Rheumatology 1991 revised criteria.^[15] All patients were referred to a reference laboratory for measurement of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Finally, DAS28 was calculated based on the formula of $\text{DAS28-ESR}; 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \log_{\text{nat}}(\text{ESR}) + 0.014 \times \text{VAS}$, and classified as in remission (<2.6), low (≥ 2.6 to <3.2), moderate (≥ 3.2 to ≤ 5.1), and high (>5.1) disease activity.

Treatment strategy

Most of the patients have been under treatment with methotrexate monotherapy or combination therapy with methotrexate plus hydroxychloroquine when they were evaluated for entering to our study. Considering response

to previous therapies, the clinician started combination therapy (or increased drugs' dose) with methotrexate (7.5 to 10 mg/week) plus hydroxychloroquine (200 to 400 mg/day) and prednisolone (2.5 to 10 mg/day) based on the clinical course. Dosage of treatment and change of the treatment for patients was registered in data gathering form. Patients were followed for 24 weeks and DAS28 was calculated with the same rheumatologist again every 12 weeks. A decrease of >1.2 score in DAS28 was defined as response.^[16]

Statistical analysis

Data were analyzed using the SPSS software for windows version 16.0. Correlation between variables was evaluated using the Pearson test if data were parametric and Spearman test if not normally distributed. Comparisons between those with and without response to treatment were done using Chi-Square test for qualitative variables and independent sample *t*-Test and Mann-Whitney test (if not normally distributed) for quantitative variables. Because the clinical response was defined based on the change in the DAS28 values, ANCOVA and regression analyses were applied to correct for the baseline DAS28 while analyzing the effect of BMI on treatment response (Δ DAS28). A *P* value of <0.05 was considered significant in all analyses.

RESULTS

Demographic data

From a total of 140 patients investigated during the study period, 19 patients were under treatment with DMARDs or drugs other than methotrexate plus hydroxychloroquine including sulfasalazine, tacrolimus, and cyclosporine. Also, 15 patients were lost to follow or had missing data. These patients were excluded from our analyses. Finally, 106 patients were included to the analyses and completely studied; (87.7% female) with mean age of 48.5 ± 13.8 years and mean disease duration of 4.4 years (SE = 0.48). Demographic data and clinical characteristics of all participants are presented in [Table 1].

Factors associated with baseline disease activity and treatment response

Including all patients, there was a negative correlation between BMI and baseline DAS28 ($r = -0.217$, $P = 0.026$). DAS28 score was decreased from 4.5 ± 1.6 to 3.3 ± 1.5 after 12 weeks of treatment ($P = 0.005$), and then was decreased to 2.9 ± 1.4 after 24 weeks from starting the treatment ($P < 0.001$). The association between BMI and Δ DAS28 after therapy was weak and not significant ($r = -0.132$, $P = 0.177$). Regarding other anthropometric measures, there was no association of waist circumference or waist to hip ratio with baseline disease activity or with Δ DAS28 after therapy [Table 2].

With regards to DAS28 components, BMI was associated with baseline VAS score ($r = -0.198$, $P = 0.040$). Also, BMI

($r = -0.301, P = 0.001$) and waist circumference ($r = -0.185, P = 0.020$) were associated with the baseline number of swollen joint [Table 2]. Regarding changes in DAS28 components after therapy, there was only a weak association between BMI and changes in ESR ($r = -0.196, P = 0.043$).

Defining response as a decrease of > 1.2 score in DAS28, comparison of responders and non-responders is presented in [Table 3]. Responders were not different from non-responders in terms of age, gender, disease duration, and anthropometric data. Although there was a trend for non-responders to be more obese (41.3% vs. 25%, $P = 0.184$) and having higher BMI (28.9 ± 5.5 vs. $27.6 \pm 4.0, P = 0.179$) than responders, this differences were not statistically significant.

Separate analysis of patients with disease duration of ≤ 2 years and > 2 years

We categorized the patients to those with disease duration of ≤ 2 years indicating early disease and those with disease duration of > 2 years. In those with early disease stage,

Table 1: Demographic data and disease characteristics of the patients

Age, year	48.5±13.9 [16 to 80]
Female/Male	93 (87.7)/13 (12.3)
BMI, kg/m ²	28.2±4.7 [18.2 to 44.9]
BMI ≥ 30 kg/m ²	34 (32.0)
Weight, kg	68.3±12.6 [39.4 to 111.0]
Waist/Hip Ratio	0.88±0.08 [0.67 to 1.11]
Disease duration, years	4.4 [SE=0.48, 2 months to 30 years]
Baseline DAS28	4.53±1.60 [2.64 to 7.65]
ESR, mm/hour	37.9±25.1 [2.0 to 130.0]
CRP	
Negative	39 (36.8)
Positive	67 (63.2)
Methotrexate starting dose, mg/week	9.6±1.8 [7.5 to 15]
Hydroxychloroquine starting dose, mg/day	187.2±34.4 [100 to 300]
Taking prednisone, n (%)	95 (89.6)

Data are presented as mean \pm SD [range] or n (%); BMI = Body mass index; DAS28 = Disease activity score in 28 joints

Table 2: Correlation of demographic data with baseline and change in disease activity

	Swollen joints	Tender joints	VAS	ESR	Baseline DAS28	DAS28 change
Age	0.118	0.108	0.071	0.019	0.058	0.052
Disease Duration	-0.099	-0.054	-0.101	-0.045	-0.058	-0.130
BMI	-0.301**	-0.105	-0.198*	-0.120	-0.217*	-0.132
Waist circumference	-0.185*	-0.029	-0.039	0.042	-0.090	-0.064
Waist/Hip Ratio	-0.031	-0.002	0.049	0.134	-0.004	0.003

Data are presented as Pearson or Spearman correlation coefficients; * $P < 0.05$ and ** $P < 0.001$ ESR = Erythrocyte sedimentation rate; BMI = Body mass index; DAS28 = Disease activity score in 28 joints; VAS = General health on a visual analog scale

analysis showed a significant and strong association of BMI ($r = -0.415, P = 0.005$) and waist circumference ($r = -0.296, P = 0.05$) with baseline DAS28. BMI was also associated with the number of swollen joints ($r = -0.415, P = 0.005$) and tender joints ($r = -0.338, P = 0.025$), and with VAS score (patient's global activity) ($r = -0.447, P = 0.002$). In this group of patients, BMI ($r = -0.337, P = 0.025$) and waist circumference ($r = -0.315, P = 0.038$) were also correlated with Δ DAS28 after therapy [Table 4]. Also, responders had higher BMI (31.0 ± 5.5 vs. 27.1 ± 4.2) and greater waist circumference (95.8 ± 11.5 vs. 87.7 ± 11.6), [Table 5]. None of the aforementioned associations or differences was present in patients with disease duration of > 2 years.

Considering the difference between responders and non-responders in baseline DAS28 and also considering correlation between BMI and baseline DAS28, ANCOVA was applied to correct for the baseline DAS28. This analysis showed no influence of BMI on Δ DAS28 ($F = 1.523, P = 0.223$). Also, a linear regression analysis controlling for age, gender, disease duration, baseline DAS28, and methotrexate, hydroxychloroquine, and prednisolone total received dose showed no association between BMI and the amount of change in DAS28 ($\beta = 0.019, 95\% \text{ CI: } -0.058 \text{ to } 0.073$), but there was a significant association between baseline DAS28 with Δ DAS28 ($\beta = 0.819, 95\% \text{ CI: } 0.714 \text{ to } 1.145$), [Table 6]. By separate insertion of waist circumference and waist to hip ratio instead of BMI into the linear regression model, there was no association between these anthropometric measures and Δ DAS28 after therapy. Also, separate linear regression analysis in

Table 3: Comparison of responders with nonresponders

	No response n = 46	Response n = 60	P
Age, year	47.8±14.3	49.0±13.6	0.654*
Female/Male	40/6	53/7	0.504**
BMI, kg/m ²	28.9±5.5	27.6±4.0	0.179*
Underweight	1 (2.1)	0	0.184**
Normal	8 (17.3)	15 (25)	
Overweight	18 (31.9)	30 (50)	
Obese	19 (41.3)	15 (25)	
Weight, kg	70.0±13.5	67.2±11.9	0.262*
Waist circumference, cm	90.6±12.9	89.3±11.5	0.599*
Waist/Hip Ratio	0.88±0.08	0.89±0.08	0.577*
Baseline DAS28	3.53±1.53	5.27±1.20	<0.001*
Disease duration, years	4.67±5.32	4.28±4.70	0.693***
Total Methotrexate, mg/week	9.9±3.3	9.4±2.4	0.523*
Total Hydroxychloroquine, mg/day	182.8±41.9	190.1±28.3	0.335*
Total Prednisolone, mg/day	4.1±2.4	5.0±2.4	0.101*
Change in DAS28	-0.21±1.19	2.89±1.10	<0.001*

Data are presented as mean \pm SD or n (%); BMI = Body mass index; DAS28 = Disease activity score in 28 joints; *Independent sample t-test; **Chi-square test; ***Mann-whitney u test

Table 4: Correlation of demographic data with baseline and change in disease activity in patients of early disease stage

	Swollen joints	Tender joints	VAS	ESR	Baseline DAS28	DAS28 change
Age	0.201	0.210	0.203	0.026	0.151	0.089
Disease Duration	0.149	0.246	0.204	0.299*	0.263	0.247
BMI	-0.415**	-0.338*	-0.447**	-0.094	-0.415**	-0.337*
Waist circumference	-0.274	-0.271	-0.286	0.038	-0.296*	-0.315*
Waist/Hip Ratio	0.083	0.013	0.033	0.048	-0.006	-0.097

Data are presented as Pearson or Spearman correlation coefficients; * $P < 0.05$ and ** $P < 0.001$; ESR = Erythrocyte sedimentation rate; BMI = Body mass index; DAS28 = Disease activity score in 28 joints; VAS = General health on a visual analog scale

Table 5: Comparison of responders with nonresponders in those with early disease stage

	No response <i>n</i> = 17	Response <i>n</i> = 27	<i>P</i>
Age, year	48.7±14.9	50.7±15.8	0.689*
Female/Male	14/3	24/3	0.426**
BMI, kg/m ²	31.0±5.5	27.1±4.2	0.013*
Underweight	0	0	0.017**
Normal	1 (17.3%)	7 (25%)	
Overweight	6 (31.9%)	15 (50%)	
Obese	10 (41.3%)	5 (25%)	
Weight, kg	75.3±13.4	66.5±10.9	0.022*
Waist circumference, cm	95.8±11.5	87.7±11.6	0.031*
Waist/Hip Ratio	0.89±0.09	0.87±0.09	0.645*
Baseline DAS28	3.21±1.45	5.32±0.99	<0.001*
Disease duration, years	1.12±0.58	1.29±0.52	0.307***
Methotrexate, mg/month	30.0±10.6	29.4±5.5	0.837*
Change in DAS28	-0.34±1.07	3.36±1.00	<0.001*

Data are presented as mean ± SD [range] or *n* (%); BMI = Body mass index; DAS28 = Disease activity score in 28 joints; *Independent sample *t*-test; **Chi-square test; ***Mann-whitney *u* test

Table 6: Linear regression analysis of factors in association with change in DAS28

	β	<i>t</i>	<i>P</i>	95.0% CI for β
Age	0.065	0.698	0.488	-0.017 to 0.035
Gender	-0.035	-0.385	0.702	-1.198 to 0.811
Disease Duration	-0.055	-0.661	0.511	-0.096 to 0.048
Baseline DAS28	0.819	8.601	<0.001	0.714 to 1.145
BMI	0.019	0.216	0.829	-0.058 to 0.073
Total received methotrexate	-0.023	-0.270	0.788	-0.126 to 0.096
Total received hydroxychloroquine	-0.049	-0.568	0.572	-0.026 to 0.014
Total received prednisolone	-0.168	-1.690	0.096	-0.274 to 0.023

BMI = Body mass index; DAS28 = Disease activity score in 28 joints

those with disease duration of ≤ 2 years and > 2 years did not change these results.

DISCUSSION

The purpose of this study was to determine if BMI or other anthropometric measures including waist circumference and waist to hip ratio are associated with disease activity and clinical response to combination therapy with methotrexate and hydroxychloroquine in RA patients. With regard to the

association between obesity and disease activity at the study entry, we found an inverse correlation of BMI with baseline disease activity. After separating patients based on disease duration, this association was only present in patients with disease duration of ≤ 2 years. The association between waist circumference and baseline disease activity was also only present in these patients. These results were similar to some previous studies that have found a possible protective role for higher BMI in RA patients at early disease stages.^[17,18] Also, we found an association of BMI with clinically swollen and tender joint counts and also with patient's global activity in early disease stage. This finding was similar to radiologic studies in patients with early RA, of up to 3-year duration, indicating the protective role of higher BMI against joint damage.^[2,19-21] However, it must be noted that BMI was no longer associated with disease activity or separately with its components in patients with disease duration of more than 2 years. This finding indicates that the possible protective effects of obesity in early RA may be diminished later in the course of the disease.^[17] Even, some studies have showed a direct association between obesity and disease activity in patients with long-time RA.^[7,22] In advanced RA, both underweight and obese states are associated with worse disease activity; an active disease lead to loss of lean body tissue and better control of the disease is associated with weight gain.^[23] Also, obesity increases the physical disability.^[24] These findings highlight the complex relationship between adiposity and obesity and clinical course in RA patients. Adipose tissue produces adipocytokines with various pro-inflammatory and anti-inflammatory effects, but the exact mechanisms behind the immune-modulatory effects of adipose tissue in RA patients are yet unexplored.^[5,17]

With regard to the effects of obesity on treatment response, we found an inverse correlation of BMI and waist circumference with the amount of change in DAS28 after therapy in patients at early disease stage. However, after controlling baseline disease activity, these correlations were no longer existed, indicating a large confounding effect of the baseline disease activity. In contrast to these results, previous studies showed a high BMI associated with less well response to anti-TNF α agents even after adjustment for the baseline disease activity. Klaasen *et al.* found that RA patients with a higher BMI have a more active disease at study entry and respond less well to infliximab.^[9] The study

by Gremese and colleagues in a larger sample of patients ($n = 641$) and longer treatment period (12 months) with anti-TNF α blockers (Adalimumab, Etanercept, and Infliximab) found no association between BMI and disease activity at baseline, but better response to infliximab in those with lower BMI and lower disease activity at baseline.^[10] In another recent study by Heimans and colleagues,^[25] 508 patients were allocated to initial monotherapy with methotrexate or combination therapy of methotrexate with prednisone or infliximab for 1 year. Authors found that higher BMI was associated with failure to achieve response (a DAS ≤ 2.4) on initial therapy with methotrexate. In this study, high BMI (≥ 25 kg/m²) was also associated with failure on delayed combination therapy with infliximab, and in the first year after starting the study, patients with a high BMI had higher DAS, worse functional ability, more tender joints and a higher VAS global health. But, high BMI in this study was not associated with more swollen joints or systemic inflammation.^[25] Differences between these findings and ours may be related to different patients' characteristics and different treatments. Patients in the mentioned studies had longer disease duration. Also, our patients had significantly higher BMI (28.2 kg/m²) compared with the mentioned studies (24.9 and 26), while disease activity score was lower in our study (4.5 vs. 5.6 and 5.9). Anyway, the exact role of BMI in response to various treatments in patients with various disease stages is yet to be clarified.

It has been suggested that the association of obesity with disease activity and response to treatment in RA patients may be due to high levels of proinflammatory cytokines produced by adipocytes.^[5,26] Waist circumferences and waist to hip ratio provide more accurate information about the body fat distribution. Hence, we evaluated these parameters to better investigate if adipose tissue has a role in creating an inflammatory and therapy-resistant state in RA patients. However, compared with BMI, we found smaller correlation coefficient of waist circumference and no association of waist to hip ratio with disease activity. In our study as well as in previous studies, BMI and waist circumference were associated with baseline swollen joint count, rather than inflammatory markers. These findings are not in favor of a mechanism involving adipose tissue-derived mediators of inflammation.^[9,25] It should be considered that clinical synovitis might be less easy to assess in RA patients with obesity and it is possible that our study as well as others underestimated joint swelling, associated with a local inflammation, in patients with a high BMI.^[25] More investigations including advanced imaging and biomarker studies are needed to further elucidate the relation between BMI and disease activity as well as treatment response.

There are some limitations to our study. The association between obesity and treatment response in our study has

been confounded by baseline disease activity. Indeed, a larger sample of patients was required for more precise evaluation of the role of obesity on various components of RA activity as well as in different disease stages, and consideration of possible confounders. Moreover, our study period was six months which, compared to other studies, was not long enough. Although, in addition to BMI, we investigated waist circumference and waist to hip ratio which provide more accurate information about the body fat distribution,^[11] these are not the most accurate measures, and also we did not evaluate adipocytokines, the hypothesized underlying mediators.

CONCLUSIONS

Our study results showed that obesity is associated with less severe disease activity in early stage of RA, but is not associated with response to combination therapy with methotrexate plus hydroxychloroquine in RA patients. However, due to our study limitations, these results should be considered with cautious. Further cohorts with larger sample size and longer follow-ups, and with more accurate investigation of body adipose composition and possible immunological mechanisms, are warranted in this regards.

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