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Impact of Gender on the Relationship Between Obesity and Inflammatory Markers in Rheumatoid Arthritis

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ABSTRACT

Background: Obesity is associated with elevated inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which can complicate disease activity assessment in rheumatoid arthritis (RA). Gender-specific differences in fat distribution and immune response may further modulate this relationship.
Objectives: To evaluate the impact of gender on the association between obesity and systemic inflammatory markers (CRP, ESR) in patients with RA in remission or low disease activity, compared to obese non-RA controls.
Methods: A cross-sectional study was conducted on 126 RA patients (70 obese and 56 non-obese) and 50 obese healthy controls. RA diagnosis was based on 2010 ACR/EULAR criteria. Patients were grouped by gender and obesity status. CRP and ESR levels were compared using Mann–Whitney U tests, with subgroup analysis by gender.
Results: Obese RA males exhibited significantly higher CRP and ESR levels compared to non-obese RA males ($p = 0.004$, 0.038, respectively). In RA females, CRP was moderately elevated in obese compared to non-obese ($p = 0.041$), while ESR differences were non-significant. Obese male controls also showed elevated inflammatory markers, suggesting adiposity-related inflammation even in the absence of RA. Overall, visceral fat in males appeared to exert a stronger influence on systemic inflammation.
Conclusion: Gender significantly influences the inflammatory response to obesity in RA. Male patients, particularly those with obesity, show disproportionately elevated CRP and ESR levels that may not reflect actual disease activity. This underscores the need for gender-specific interpretation of inflammatory markers to avoid misclassification and overtreatment in RA.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 0.5–1% of the adult population worldwide. It is characterized by systemic inflammation and progressive joint destruction, leading to disability and increased morbidity. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are routinely used in clinical practice to assess disease activity and monitor treatment response. These markers also form part of composite indices such as the Disease Activity Score-28 (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) [1].

However, CRP and ESR are nonspecific and influenced by various non-disease-related factors such as age, infection, and particularly, obesity. Obesity is associated with a chronic, low-grade inflammatory state mediated by adipose tissue-derived cytokines such as IL-6, TNF-α, and leptin [2] [3]. IL-6, in particular, stimulates hepatic CRP production, making CRP levels

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susceptible to elevation in obese individuals regardless of autoimmune disease activity [4]. Wellen and Hotamisligil have described adipose tissue as an active immunologic organ contributing to systemic inflammation [5], and Tilg and Moschen emphasized the concept of "adipocytokines" — hormones from fat tissue that affect immune responses in chronic inflammatory diseases like RA [3].

Several studies have demonstrated the confounding effect of obesity on inflammatory markers in RA patients. Giles et al. found that CRP levels were significantly elevated in obese RA patients in clinical remission, suggesting misclassification of disease activity [6].

George et al. confirmed that both CRP and ESR levels were influenced by adiposity, especially in obese patients with low disease activity [7]. Dessein et al. also reported significant associations between BMI and CRP in RA, regardless of joint activity [8].Moreover, increasing attention is being given to gender-based differences in fat distribution and inflammation. Men tend to accumulate visceral fat — more metabolically active and inflammatory — while women predominantly store subcutaneous fat, which is less immunologically active [9][10].Fried et al. showed that visceral adiposity correlates more strongly with inflammatory cytokines in males than in females [10]. This difference may alter the way obesity affects CRP and ESR levels across sexes in RA.

Therefore, this study aims to investigate the gender-specific impact of obesity on inflammatory markers in RA patients with low disease activity or remission. We hypothesize that obesity raises CRP and ESR disproportionately in males due to greater visceral fat and IL-6-driven inflammation. Better understanding of this effect is critical to avoid overtreatment and to improve precision in RA disease activity interpretation.

Methods

Study Design and Population

This was a cross-sectional, observational study conducted at Baghdad Teaching Hospital, including adult patients diagnosed with rheumatoid arthritis (RA) and a group of healthy obese individuals as controls. The study was approved by the institutional ethical committee, and written informed consent was obtained from all participants.

A total of 126 RA patients were enrolled. All patients met the 2010 ACR/EULAR classification criteria for RA (Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010) and were in clinical remission or low disease activity, defined as a Clinical Disease Activity Index (CDAI) score of less than 10. In addition, 50 age- and sex-matched healthy obese individuals without RA or other inflammatory conditions were recruited consecutively as a control group.

Inclusion and Exclusion Criteria

Inclusion criteria for RA group:

- Adults aged 18–70 years
- Fulfilled the 2010 ACR/EULAR RA classification criteria
- CDAI score <10
- Stable on current RA treatment regimen for at least 3 months

Exclusion criteria:

- Active infection or recent surgery
- Known malignancies
- Chronic kidney or liver disease
- Other autoimmune or systemic inflammatory conditions
- Pregnancy
- Use of systemic corticosteroids >10 mg/day

ISSN 3106-5430 (print)

Data Collection

Demographic data (age, sex), disease duration, BMI, and medication use were recorded. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Patients were categorized as obese (BMI ≥30 kg/m^2) or non-obese (BMI <30 kg/m^2) based on WHO criteria. RA patients were further stratified by sex and obesity status.

Laboratory Tests

Venous blood samples were collected from all participants to measure:

C-reactive protein (CRP): using colorimetric principle (LAMBERT-BEER law) in milligrams per deciliter (mg/dl).

Erythrocyte sedimentation rate (ESR): using the Westergren method in millimeters per hour (mm/h).

All laboratory analyses were performed in the hospital's central laboratory using standardized procedures.

Statistical Analysis

Statistical analysis was performed using SPSS software version 25. Continuous variables were expressed as median and interquartile range (IQR) due to non-normal distribution. Comparisons between groups were conducted using the Mann–Whitney U test due to non-normal distribution (The Mann–Whitney U test (also known as the Wilcoxon rank-sum test) is a non-parametric statistical test used to compare differences between two independent groups when the data do not follow a normal distribution). A p-value <0.05 was considered statistically significant.

Patients were grouped into:

Obese male RA patients
Non-obese male RA patients
Obese female RA patients
Non-obese female RA patients
Obese healthy male controls
Obese healthy female controls

Primary comparisons included CRP and ESR levels across these gender–obesity subgroups.

Result

Demographic and Clinical Characteristics

Age

A total of 126 RA patients (70 obese, 56 non-obese) and 50 obese healthy controls were enrolled. The mean age of RA patients was 46.1 ± 10.5 years (range: 26–67), and for obese controls was 43.7 ± 9.5 years (range: 24–62). Age distribution was comparable between groups, as shown in **Figure 1.**

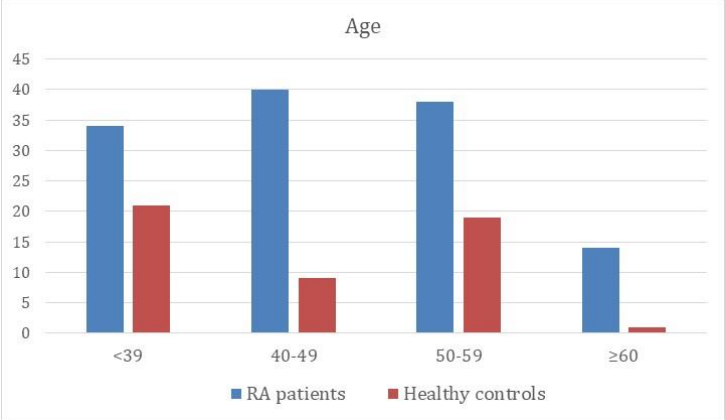

Figure 1. Age Distribution by Study Groups

ISSN 3106-5430 (print)

Gender

Among the RA cohort, 76.2% (n=96) were female and 23.8% (n=30) were male, yielding a female-to-male ratio of approximately 3.2:1. This reflects the known female predominance in RA. Gender distribution among RA patients is illustrated in **Figure 2**.

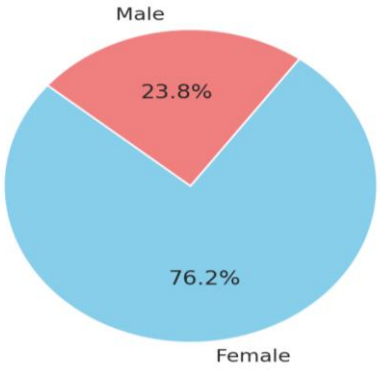

Figure 2. Gender Distribution among RA Patients

Medications

Most patients were on biologic disease-modifying antirheumatic drugs (bDMARDs), either alone or in combination. Approximately 66% were receiving bDMARD monotherapy. Methotrexate (MTX), hydroxychloroquine (HCQ), and prednisolone (PND) were used in varying frequencies. These data support that participants were managed under current RA treatment guidelines.

Baseline Clinical and Laboratory Characteristics

Table 1 summarizes the demographic and laboratory profiles across six groups: obese RA males, non-obese RA males, obese RA females, non-obese RA females, obese control males, and obese control females.

Notably, median CRP and ESR were higher in obese RA males (CRP: 5.8 mg/L; ESR: 28 mm/hr) compared to their non-obese male counterparts (CRP: 2.7 mg/L; ESR: 16 mm/hr), highlighting the influence of obesity on systemic inflammation, particularly in males. A similar, though less pronounced, pattern was observed in females. Among obese healthy controls, CRP and ESR levels were moderately elevated despite the absence of RA, with higher values in males than females.

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Study Groups

Characteristic	Obese RA Males	Non-Obese RA Males	Obese RA Females	Non-Obese RA Females	Obese Control Males	Obese Control Females
Number of patients, n (%)	18 (25.7%)	12 (21.4%)	52 (74.3%)	44 (78.6%)	20 (40%)	30 (60%)
Median age (years)	51	49	51	48	48	47
Median disease duration (years)	6.5	5.5	6.5	5.5	—	—
Median BMI (kg/m²)	32.9	27.1	32.4	26.7	30.5	29.8
Median CRP (mg/L)	5.8	2.7	5.1	3.8	4.6	3.9
Mean CRP (mg/L)	6.1	3.0	5.4	4.0	4.8	4.1
Median ESR (mm/hr)	28	16	26	21	22	19
Mean ESR (mm/hr)	30.2	17.5	27.4	22.1	23.3	19.8

RA: rheumatoid arthritis; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

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Comorbidities of RA Patients

Among the RA patients, 39 were found to have one or more chronic comorbidities. Hypertension was the most prevalent, followed by diabetes mellitus. The distribution of chronic diseases across non-obese and obese RA patients is presented in Table 2.

Table 2. Comorbidities of RA Patients

Variables	Non-obese RA (n=56)	Obese RA (n=70)	Total (n=126)
Hypertension	Yes: 13 (23%)	Yes: 19 (27%)	Yes: 32 (25%)
	No: 43 (77%)	No: 51 (73%)	No: 94 (75%)
Diabetes mellitus	Yes: 6 (11%)	Yes: 22 (31%)	Yes: 28 (22%)
	No: 50 (89%)	No: 48 (69%)	No: 98 (78%)
Ischemic heart diseases	Yes: 0 (0%)	Yes: 4 (6%)	Yes: 4 (3%)
	No: 56 (100%)	No: 66 (94%)	No: 122 (97%)
Respiratory diseases	Yes: 0 (0%)	Yes: 2 (3%)	Yes: 2 (2%)
	No: 56 (100%)	No: 68 (97%)	No: 124 (98%)
Thyroid diseases	Yes: 2 (4%)	Yes: 0 (0%)	Yes: 2 (2%)
	No: 54 (96%)	No: 70 (100%)	No: 124 (98%)
Epilepsy	Yes: 0 (0%)	Yes: 1 (1%)	Yes: 1 (1%)
	No: 56 (100%)	No: 69 (99%)	No: 125 (99%)

Sociodemographic Data of RA Patients

The RA patients showed diverse sociodemographic backgrounds. Educational attainment varied from illiteracy to university-level education. Most patients were non-smokers and lived in urban areas. Table 3 summarizes the sociodemographic characteristics of the RA patients.

Table 3. the sociodemographic characteristics of the RA patients.

Variables	Non-obese RA (n=56)	Obese RA (n=70)	Total (n=126)
Educational Level			
Illiterate	11 (20%)	17 (24%)	28 (22%)
Primary	11 (20%)	19 (27%)	30 (24%)
Secondary	15 (27%)	19 (27%)	34 (27%)
University	19 (34%)	15 (21%)	34 (27%)
Smoking Status			
non-smoker	44 (79%)	54 (77%)	98 (78%)
current smoker	8 (14%)	6 (9%)	14 (11%)
Ex-smoker	4 (7%)	10 (14%)	14 (11%)
Residential setting			
Urban	50 (89%)	60 (86%)	110 (87%)
Rural	6 (11%)	10 (14%)	16 (13%)

Gender-Based Comparison of Inflammatory Markers

Mann–Whitney U tests were conducted to assess the impact of gender on the relationship between obesity and inflammatory markers in RA patients and controls. Among males, CRP and ESR levels were significantly higher in obese RA patients compared to non-obese RA males (CRP $p = 0.0038$, ESR $p = 0.0401$). Similarly, obese RA males had significantly elevated CRP and ESR compared to obese control males (CRP $p = 0.0044$, ESR $p=0.0002$).

Among females, obese RA patients had significantly higher CRP than their non-obese counterparts ($p = 0.0250$), but the difference in ESR was not statistically significant ($p =$

ISSN 3106-5430 (print)

0.4697). However, ESR was significantly elevated in obese RA females when compared to obese healthy females (p = 0.0001), while CRP levels were not significantly different (p = 0.4648). These findings reinforce the gender-specific influence of obesity on systemic inflammation in RA. See detailed results in Table 4 below.

Table 4: Mann–Whitney U test results comparing CRP and ESR between RA and control groups by gender

Group Comparison	CRP (mg/L) p-value	ESR (mm/hr) p-value
Obese RA Male vs Non-Obese RA Male	0.0038	0.0401
Obese RA Female vs Non-Obese RA Female	0.0250	0.4697
Obese RA Male vs Obese Control Male	0.0044	0.0002
Obese RA Female vs Obese Control Female	0.4648	0.0001

Discussion

The demographic and clinical characteristics of the study participants align with previous findings in the literature. The mean age of RA patients in our study was 46.08 ± 10.5 years, which is comparable to results from other studies conducted in Iraq and the region, where mean ages typically range from 45 to 50 years [13][14].The female predominance (76.2%) with a female-to-male ratio of 3.2:1 is also consistent with known RA epidemiology, where the disease is two to four times more common in females than males [15].The majority of our patients had long-standing disease and were under biologic therapy, reflecting the current trend of aggressive early intervention and the increasing use of biologics in routine practice [16].BMI values showed a considerable proportion of patients in the obese category, in line with data suggesting increasing obesity prevalence among RA populations globally [17].This highlights the importance of evaluating the impact of adiposity on disease markers and activity scoring, especially in remission phases.

This study demonstrates a clear gender-specific influence of obesity on systemic inflammation in patients with rheumatoid arthritis (RA) in clinical remission or low disease activity. The results highlight that obese male RA patients exhibit significantly higher CRP and ESR levels than their non-obese counterparts, as well as compared to obese healthy males. In contrast, obese RA females showed significant differences in CRP compared to non-obese RA females, but ESR changes were not statistically significant.

These findings are consistent with previous studies showing that obesity leads to elevated inflammatory markers, which can confound the assessment of RA activity. Giles et al. reported elevated CRP levels in obese RA patients despite clinical remission, suggesting adiposity-related inflammation may mimic active disease and contribute to overtreatment if not recognized properly [6].George et al. and Dessein et al. also confirmed a direct relationship between BMI and inflammatory markers, independent of joint involvement [7][8].

The gender disparity observed in this study supports the hypothesis that visceral adiposity, more prevalent in males, may generate stronger pro-inflammatory cytokine responses — particularly interleukin-6 (IL-6), which in turn stimulates CRP production [3][4].Fried et al. found that men tend to accumulate more visceral fat, which is metabolically active and secretes greater levels of IL-6, while women typically have more subcutaneous fat, which is less inflammatory [10].

ISSN 3106-5430 (print)

The finding that ESR was significantly higher in obese female RA patients compared to obese healthy females may reflect an additive effect of RA-associated inflammation and obesity, although the CRP levels did not show a corresponding rise. This underscores that gender-specific fat distribution and its impact on inflammation must be considered when interpreting laboratory markers.

Furthermore, among obese control males without RA, CRP and ESR levels were comparable to those seen in male RA patients in remission, which reinforces the hypothesis that obesity can elevate inflammatory markers independently of RA disease activity. This presents a challenge in clinical practice: using CRP and ESR as part of composite disease activity scores (e.g., DAS28) may overestimate inflammation in obese males and result in unnecessary treatment escalation.

The results emphasize the need for gender- and BMI-adjusted interpretation of inflammatory markers in RA. Clinicians should consider these confounding factors, especially when treating patients in apparent clinical remission.

This study has several limitations that should be acknowledged. First, its cross-sectional design limits the ability to establish causal relationships between obesity, gender, and inflammatory markers. Longitudinal studies would be more suitable to assess temporal changes and causality. Second, although we used CRP and ESR as standard markers of systemic inflammation, we did not assess specific adipokines (such as IL-6, TNF-α, or leptin), which could have provided mechanistic insights into the observed gender differences. Third, the sample size, especially for male subgroups, was relatively small, which may limit statistical power and the generalizability of the findings. Fourth, visceral and subcutaneous fat distribution was not directly measured (e.g., via imaging or waist–hip ratio), which could have strengthened the analysis of gender-specific fat depots and inflammation. Fifth, lifestyle factors such as physical activity, diet, and socioeconomic status — all of which may influence both obesity and inflammatory markers — were not comprehensively assessed. Finally, although controls were recruited consecutively and matched for age and sex, they may still differ from RA patients in unmeasured variables that could confound the results.

Conclusion

This study highlights the significant influence of gender on the relationship between obesity and inflammatory markers in patients with rheumatoid arthritis. Elevated CRP and ESR levels in obese male RA patients—despite clinical remission—suggest that adiposity-related inflammation, particularly visceral fat-driven cytokine activity, can mimic active disease. In contrast, obese female RA patients demonstrated a milder inflammatory response, indicating a possible protective effect of subcutaneous fat distribution.

These findings underscore the importance of incorporating both gender and BMI considerations when interpreting CRP and ESR values in RA patients, especially those in remission or low disease activity. Failure to do so may lead to overestimation of disease activity and inappropriate treatment escalation. Gender-specific thresholds for inflammatory markers may improve the accuracy of RA assessment and help tailor therapeutic decisions more effectively.

Further longitudinal and mechanistic studies are warranted to validate these observations and guide the development of personalized disease activity metrics in RA.

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Conflict of Interest

The authors declare no conflict of interest.

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