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The Impact of Obesity on Inflammatory Markers Used in the Assessment of Disease Activity in Rheumatoid Arthritis

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Abstract: ***Background: Rheumatoid arthritis (RA) is a systemic inflammatory disorder in which raised C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are indicators of active disease. Obesity can falsely raise acute phase reactants in obese patients with RA, independent of disease activity. Objectives: to study the obesity effect on the levels of CRP and ESR among patients with rheumatoid arthritis in low disease activity or remission state. Patients and Methods: A cross-sectional study was conducted at the Rheumatology Unit of Baghdad Teaching Hospital in 2023. The study included 126 adult rheumatoid arthritis patients (70 obese and 56 non-obese), that had previously been diagnosed by a rheumatologist (according to the 2010 American College of Rheumatology criteria/ European League Against Rheumatism). The participants were aged ≥ 18 years and with CDAI < 10, and 50 obese healthy controls. Demographic and disease characteristics of patients were collected. Results: the mean age for RA patients and obese healthy controls was comparable. The F: M ratio of study participants was 3.2: 1. RA obese patients had significantly higher mean CRP levels than non-obese patients, while the differences of elevated ESR in both groups were insignificant, while the differences in ESR level between obese RA patients and obese healthy controls was significant, unlike CRP level differences between the two groups were insignificant. Conclusion: Obesity may falsely elevate CRP and ESR in RA patients with low disease activity or remission states by 25% and 10% respectively. Clinicians must be cautious while treating such patients.***

Keywords: Rheumatoid arthritis, obesity, Creactive protein, erythrocyte sedimentation rate, inflammation

1. Introduction

Definition and epidemiology of RA:

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune inflammatory diseases (1) . RA affects the joints, particularly the small joints in the hands and feet, causing joint damage and bone destruction. This can result in severe impairment. RA affects 5 to 10 out of every 1, 000 persons worldwide. The highest incidence of RA is found in those between the ages of 65 and 74. Women are affected 2 to 3 times more than men at any age. Besides women, smokers, and people with a family history of RA are more at risk of developing the disease (2, 3) . The prevalence of R A among Iraqi adults was estimated to be 1% of those aged 16 years and over representative of differences in geography and ethnicity (4) .

Treatment of RA:

Initiating pharmacotherapy soon after the onset of RA reduces the progression of joint damage and improves long-term outcomes. The EULAR therefore recommends that treatment with a disease-modifying antirheumatic drug (DMARD) should be initiated as soon as a diagnosis of RA is made (5) .

The combination of biologics plus methotrexate gives better disease control than the use of single treatment alone (6) .

Obesity:

There are several possible mechanisms leading to obesity. The traditional view is that there is significantly more energy stored vs energy used (by the body). The excess energy is stored in fat cells, thereby developing the characteristic obesity pathology (7) . An exorbitant accumulation of adipose tissue in the body characterizes the phenomenon of obesity (8) .

In the past decades, obesity has become a major worldwide health problem (9) . The prevalence of obesity has been rising. It is estimated that around 1, 2 billion adults, this is approximately 1 out of 7 of the global population, are overweight or suffer from obesity (10) .

Due to the close association of obesity with activation of pro-inflammatory pathways, obese RA patients may have more active and severe disease states. It has been shown that white adipose tissue is a source of specific adipocytokines (e. g., leptin, resistin, adiponectin, and visfatin) that are increased in RA patients and are able to increase the expression of cytokines such as tumor necrosis factor alpha and interleukin-6 (11) . We need to explore the hypothesis that obese RA patients have higher CRP and ESR than non-obese RA patients.

Objectives:

The objective was to study the frequency of the confounding effect of obesity on the levels of CRP and ESR in patients

with rheumatoid arthritis in low disease activity state or remission, using the clinical disease activity index (CDAI).

2. Patients and Methods

Study design:
A cross-sectional study was carried out amongst RA patients at the Rheumatology Unit of Baghdad Teaching Hospital/ Medical City from January 2023 until the end of September 2023. A total of 126 consecutive eligible patients, and 50 obese healthy controls were studied.

Study population:

Inclusion criteria:
Adult RA patients (2010 ACR/ EULAR criteria) ≥ 18 years, and with CDAI < 10, regardless of gender or duration of disease, who were attending the outpatient rheumatology clinic for follow-up, and those who were attending the hospital for treatment and follow-up were recruited into the study. The study included RA patients who were receiving (csDMARDs, bDMARDs) whether they were in a condition of remission or low disease activity state. Assessment of Clinical Disease Activity Index (CDAI) which consists of four criteria; the patient global assessment and the evaluator global assessment both using visual analogue scale, and the number of tender and swollen joints. The numerical summation ranges from zero (best score) to 76 (worst score). The CDAI is one of the best tools to evaluate clinical remission of the disease. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Exclusion criteria:
Exclusion criteria included any present or recent infection, major surgery during the previous three months, and presence of another inflammatory condition. (e. g.: rheumatoid vasculitis, scleritis/episcleritis, chronic obstructive pulmonary disease, malignancy, pregnancy, liver diseases, anemia (hemoglobin < 10 g/dl), polycythemia (hemoglobin > 16.5 g/dl), or overlap with any other connective tissue disease).

Data collection:
Eligible patients were recruited from patients attending the rheumatology clinic in Baghdad Teaching Hospital. Data was recorded using a Google form that captured general demographic data (age, gender, education level, smoking state, residential setting, height, and weight), disease duration, their current treatment, and comorbidities: hypertension, Diabetes Mellites, ischemic heart diseases, hyperlipidemia, respiratory disorders, renal disorder, liver disorder, endocrine disorder, heart disorder and cancer.

CRP and ESR levels were measured in all study participants. CRP was measured by colorimetric principle (LAMBERT-BEER law), in milligrams per deciliter (mg/dl), and ESR measured by Westergren's method, in millimeters per hour (mm/h).
According to WHO classification (12) , BMI of adults > 20 years old has been classified into following categories:

<18.5	Underweight
18.4-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Obese
>35.0	Severe obesity

Two groups of patients were defined: Obese RA group comprising 70 obese RA patients defined by BMI of ≥ 30. Non-obese RA group comprising 56 non-obese RA patients (BMI < 25). The study also included a third (control) group of 50 'healthy' obese individuals (BMI ≥30) who did not have RA.

Ethical approval:
The study protocol was approved by supervising committee of the Iraqi Board for Medical Specializations, with approval number 194 on the 16th of January 2023. Verbal consent was obtained from each participant included in the study according to the declaration of Helsinki.

Statistical analysis:
Data was analyzed using the Statistical Package for Social Sciences-version 26 (SPSS-v26), and presented in simple measures of frequency, percentage, median, mean, standard deviation (SD), and range (minimum-maximum values).
The statistical significance of the differences in ESR and CRP levels between obese RA and non-obese RA groups, as well as between obese RA and obese 'healthy' control groups was assessed using Mann-Whitney U test. Statistical significance was set at $p \leq 0.05$.

3. Results

Demographic and clinical data:

Age:
This study included 126 adult RA patients, their mean age and standard deviation was (46.08± 10.515) and ranged between (26-67) years and 50 obese 'healthy' controls, their mean age and standard deviation was (43.68± 9.529) and ranged between (24-62).

Sex:
The majority of study patients were females 96 (76.2%), while male patients were 30 (23.8%). The F: M ratio was 3.2: 1.

Medications:
The majority of study patients (66%) were on biologics as monotherapy, frequencies and percentages of other medications are shown in figure 1.

Baseline characteristics of patients and controls:
A total of 126 RA patients, [70 obese RA patients (50 F, 20M), 56 non-obese RA patients (46 F, 10 M)], and 50 obese 'healthy' controls (40 F, 10 M) were enrolled into the study (Table 1).

In all the three groups, mean BMIs were 33.93, 23.50, and 36.05 kg/m^2, respectively, median CRP levels were 4.8 (IQR 3), 3.2 (IQR 2.9) and 4.05 (IQR 5.5) respectively, while median ESR was 35 (IQR 25), 31 (IQR 24) and 13 (IQR 18) respectively. Mean CRP of obese RA patients was (4.81 ±1.92) and mean ESR was (36.49 ±19.35). While mean CRP in non-obese RA patients was (3.92 ±3.56) and mean ESR

was (31.61 ±15.98). In obese healthy control mean CRP was (5.52±5.03) and mean ESR was (17.48±16.11).

Comorbidities of RA patients:
Thirty nine of the studied patients had chronic diseases, with hypertension being the most common comorbidity as shown in table 2.

Sociodemographic data of RA patients:
Patients had different educational levels [illiterate 28 (22%), primary school 30 (24%), secondary school 34 (27%) and university 34 (37%)]. Regarding smoking status [non-smoker 98 (78%), current smoker 14 (11%) and ex-smoker 14 (11%)].110 (87%) of patients lived in urban areas and 16 (13%) lived in rural areas. All sociodemographic data are shown in table 3.

The differences in ESR and CRP levels between obese and non-obese RA patients:
The current study showed obese RA patients had statistically significant elevation of CRP levels compared to non-obese RA patients (p values < 0.001) and non-significant for ESR (p value=0.157) as shown in table 4. (were analyzed using Mann-Whitney U test).

The differences in ESR and CRP levels between obese healthy controls and obese RA patients:
Our study showed that there are significant differences in ESR levels between obese 'healthy' controls and obese RA patients (p value < 0.001), unlike CRP levels which were non-significant (p value=0.179) as shown in table 5. (were analyzed using Mann-Whitney U test).

The differences in ESR and CRP levels between females and males in RA patients' groups:
The differences in CRP levels between non-obese and obese RA patients were significant for females (p value=0.025), while in ESR levels, they were not significant (p value=0.467). For males, the differences in CRP and ESR levels were significant (p value 0.004 and 0.038, respectively) (Table 6). (was analyzed by Mann-Whitney U test).

The differences in CRP levels between 'healthy' controls and obese RA patients among females and males were non-significant (p value 0.072 and 0.940 respectively). while the differences in ESR levels among females and males were significant (p value <0.001 and 0.011 respectively).

4. Discussion

RA is a systemic inflammatory disease in which elevated CRP and ESR indicate active disease. Additionally, acute phase reactants are used to monitor RA patients and evaluate how well they are responding to treatment. Infection and inflammation lead to an increased acute phase reactants. They are significant components of numerous composite indices used to assess RA disease activity. Obesity has been linked to higher CRP and ESR levels in the general population (13) . Obesity can cause an increase in acute phase reactants in obese RA patients regardless of disease activity (14) . This could lead to falsely elevated disease activity tool results, that contain acute phase reactants in their calculation. Consequently, it will be difficult to accurately assess the level of disease activity.

Obesity and inflammatory markers are correlated in RA patients, according to published series, regardless of disease activity. Few studies investigated the frequency of this confounding impact (15) . This study was carried out to determine how frequently obesity is associated with high inflammatory markers among RA patients in remission or low disease activity state.

The present study showed that RA patients' age mean, and standard deviation was (46.08±10.515) and ranged between (26-67) years, this distribution of age groups among RA patients was observed in two other studies done in Iraq by Mahmood Abdullah R *et al.* whose patients mean age and SD was (43.76±12.64) and range 20-60 years, and by Al-Rawi ZS *et al.* whose patients mean age and SD was (46.53±11.89) years (16, 17) .

The results of our study showed female to male ratio of 3.2: 1 which agrees to the general concept of sex distribution in RA similar to the findings of an earlier Iraqi study by Alrawi ZS *et al.* which reported F: M ratio of 3: 1 (18) . This was in line with the study done in Egypt by Abd-Elazeem MI *et al.* (19) .

Female predominant in RA patients are well explained by the effects of estrogen and some data potentiate the concept of immune system modulation by hormone, for example: exposure of autoantibody producing B lymphocytes to estradiol makes them to be more resistant to programmed cell death (apoptosis), suggesting autoreactive B lymphocytes clones could avoid immune tolerance (20) .

The current study showed that obese RA patients had significantly higher CRP levels compared to non-obese RA patients. This is consistent with a study done in India by Sharma A *et al* 2020 (15) and an observational study from USA by George *et al.*2018 (14) that showed obese RA patients had significantly higher CRP levels than non-obese RA patients. While difference in CRP level of elevation between obese RA patients with CDAI <10 (low disease activity/remission state) and obese 'healthy' controls was non-significant, which in both of them attributed to obesity as primary cause of CRP elevation.

The present study also showed that there was no significant difference in ESR levels when comparing obese RA patients with that of non-obese RA patients. This disagrees with the study done in Egypt by Ellabban *et al.*2016 which showed that the correlation between BMI and CRP, ESR, RF, and serum triacylglyceride was highly significant (21) .

Our study showed that obese RA patients had a significantly higher ESR than obese 'healthy' controls which is consistent with the study by Sharma A *et al.*2020 (15) .

In our study, obesity was related with significantly increased CRP and ESR in male RA patients, and this disagreed with the study by George *et al.*2017 (14) where it found that obesity is associated with higher ESR and CRP in female RA patients. The cause might be the visceral fat (fat

surrounding internal organs) has a higher effect on the liver production of CRP than truncal fat. In all previous studies, DEXA was utilized to measure truncal fat, or an evaluation of visceral fat using abdominal computed tomography (CT) may eliminate the discrepancy between acute phase reactants and obesity that is seen in female RA patients.

Patients with remission or low disease activity state haven't been included in any of the aforementioned studies except for Sharma A *et al.* (15) . These studies, however, made an adjustment for disease activity. We chose patients in remission or with low disease activity to effectively exclude active disease as the reason of the elevated acute phase reactants. However, some patients may have had subclinical inflammation, which may have contributed to elevated CRP or ESR. Subclinical inflammation can be detected using ultrasound and MRI (22, 23) .

Furthermore, we have used strict exclusion criteria to rule out other possible causes of raised inflammatory markers. We ruled out patients taking tocilizumab since it lowers the synthesis of CRP in the liver, which directly lowers CRP levels.

This study had some limitations however. A single tertiary center was involved in the study. Furthermore, there is no assessment of visceral fat mass (by abdominal CT) or truncal fat mass (detected by DEXA). It is important to note that there is no standardized definition of obesity when using imaging to assess body fat. Limited number of studies assessing the impact of obesity on inflammatory markers in RA patients, thus, the comparison of these results with previous researches was limited.

5. Conclusions

When treating RA patients using a "treat-to-target" strategy, clinicians should take caution, whereby acute phase reactants are used as one of the components of disease activity score. At the present time, when there are several RA treatment options available (including biological DMARDs), to avoid overtreatment, drugs must be used judiciously.

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Conflict of interest
The authors declare that there are no conflicts of interest.

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Tables and Figure

Table 1: Characteristics of patients and healthy control

Variables	Obese RA group (n= 70)	Non-obese RA group (n = 56)	Obese healthy controls group (n = 50)	P. value
Mean age in years (SD)	46.31 (9.53)	45.79 (11.71)	43.68 (9.52)	0.453
Number of males (%)	20 (28.6)	10 (17.9)	10 (20.0)	0.312
Number of females (%)	50 (71.4)	46 (82.1)	40 (80.0)	
Mean disease duration (years)	7.21	6.70		0.601
Mean BMI (kg/m2)	33.93	23.50	36.05	
Median CRP (IQR)	4.8 (3.0)	3.2 (2.9)	4.05 (5.5)	
Median ESR (IQR)	35 (25)	31 (24)	13 (18)	
Mean CRP (SD)	4.81 (1.92)	3.92 (3.56)	5.52 (5.03)	
Mean ESR (SD)	36.49 (19.35)	31.61 (15.98)	17.48 (16.11)	

Table 2: Chronic diseases among study patients

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

Table 3: Sociodemographic data of RA patients

Variables		Non-obese RA frequencies (%)	Obese RA frequencies (%)	Total frequencies (%)
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)

Table 4: The differences in ESR and CRP levels between obese and non-obese RA patients

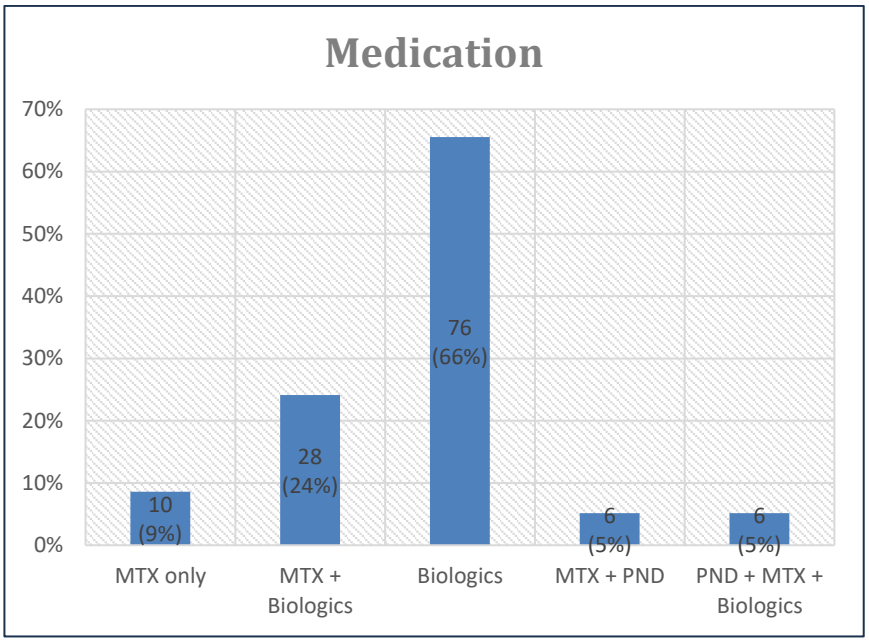
Variable	Obese RA	Non-obese RA	P. Value
Median CRP (mg/dl)	4.8	3.2	<0.001
Median ESR (mm/h)	35	31	0.157

Table 5: The differences in ESR and CRP levels between obese healthy controls and obese RA patients

Variable	Obese RA	Obese healthy controls	P. Value
Median CRP (mg/dl)	4.8	4.05	0.179
Median ESR (mm/h)	35	13	<0.001

Table 6: The differences in ESR and CRP levels between females and males in RA patients' groups

Variable	Obese RA females	Non-obese RA females	P. Value
Median CRP (mg/dl)	4.5	3.5	0.025
Median ESR (mm/h)	34	23	0.467
Variable	**Obese RA males**	**Non-obese RA males**	**P. Value**
Median CRP (mg/dl)	3.5	1.7	0.004
Median ESR (mm/h)	40	19	0.038



MTX=Methotrexate, PND=prednisolone, Biologics=bDMARDs

Figure 1: Distribution of study patients by medication used