

Prevalence of Obesity in A Cohort of Egyptian Rheumatoid Arthritis Patients and Its Implication on Disease Activity

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease with articular and extra-articular manifestations, several factors can affect disease outcome.

Objective: To assess the prevalence of obesity in a cohort of Egyptian rheumatoid arthritis patients and study its relation to disease activity and extra-articular manifestations.

Patients and methods: The study included 200 RA patients. Detailed medical history, disease activity score (DAS28), VAS, HAQ, were carefully recorded. High-resolution computed tomography (HRCT) was done and to detect lung affection. BMI was calculated and patients were sub-grouped accordingly into underweight, normal BMI, over-weight and obese patients.

Results: Patients were 172 females and 28 males with a mean age of 45.1±14.2 years. According to BMI, 32% of patients were overweight, 35% were obese, 20% with normal BMI and 13% were underweight. Overweight and obese patients were significantly older ($p < 0.001$), had longer disease duration ($p < 0.001$), had higher ESR, CRP, DAS, HAQ, VAS ($p < 0.001$), had more frequent arthritis ($p < 0.001$), had joint deformity, had rheumatoid nodules ($p = 0.007$) and ILD ($p < 0.001$).

Conclusion: overweight and obesity were frequent among Egyptian RA patients. It was associated with high disease activity and extra-articular manifestations. In turn, patients' weight reduction can help in improvement of patients' outcome and disease activity control.

Keywords: Obesity, Rheumatoid arthritis, Extra-articular.

INTRODUCTION

Rheumatoid arthritis (RA) is a common multisystem connective tissue disease of autoimmune nature ⁽¹⁾. Approximately It affects 0.5- 1% of the general population, with high female predominance. Usually it is characterized by the presence of additive polyarthritis affecting large and small joints with specific predilection of small joint of the hands with high tendency of joint destruction. Approximately 50% of rheumatoid patients have extra-articular manifestations with lung affection, infection and accelerated atherosclerosis being significant causes of morbidity and mortality in these patient ⁽²⁾. Symptoms of RA can vary from, such as pain, stiffness and swelling up to sever joint disabilities. Extra-articular manifestations may be life threatening ⁽¹⁾. Importantly, persistently high disease activity without proper control is associated with irreversible joint destruction and reduction of life expectancy ⁽¹⁾.

Treatment of RA patients should be started as early as possible to avoid joint deformities and severe disabilities. Management of RA requires repeated assessment of disease activity using different activity measures ⁽³⁾. Several disease activity scores are available to asses RA disease activity; Disease Activity Score in 28 joints (DAS28-ESR) ⁽⁴⁾, the Simplified Disease Activity Index (SDAI) ⁽⁵⁾ and the Clinical Disease Activity Index (CDAI) ⁽⁶⁾. These are the disease activity indices that are most frequently used in RA, which generate specific cut-off values that are used

to classify RA as in remission or in a low, moderate, or high activity state ⁽⁴⁾.

Overweight and obesity with a state of increased white adipose tissue are characterized by a state of low-grade inflammation. Adipose tissues secrete a wide range of several inflammatory mediators such as leptin, tumor necrosis factor alpha (TNF-alpha), IL-6 and monocyte chemotactic proteins ⁽⁷⁾. Several studies in the literature reported that obesity could be considered a documented risk factor for development of RA ⁽⁸⁾. Some researchers reported that obese or overweight RA patients are less likely to achieve disease remission. Moreover, obesity can reduce the probability of patients' response to anti – TNF drugs ⁽⁹⁾.

Current study aimed to assess prevalence of obesity in a cohort of Egyptian rheumatoid arthritis patients and its relation to disease activity and extra-articular manifestations.

PATIENTS AND METHODS

This cross sectional study included 200 RA patients fulfilling the American College of Rheumatology and European League against Rheumatism (ACR/EULAR) 2010 classification criteria ⁽¹⁰⁾. Patients were recruited from Outpatient Rheumatology Clinic and Inpatient Department of Rheumatology Ain Shams University Hospital during the period from March 2018 to May 2020. Patients with other connective tissue diseases, malignancy, diabetes



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mellitus and age <18 years were excluded from the study.

Demographics, clinical manifestations and medication history were carefully recorded. Disease activity score (DAS28) was assessed and graded as remission (≤ 2.6), low (≤ 3.2), moderate (3.2-5.1) and high (≥ 5.1)⁽⁴⁾. Laboratory investigations included complete blood picture (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), kidney function tests, liver enzymes, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP). Functional disability was assessed using Health Assessment Questionnaire (HAQ)⁽¹¹⁾ and fatigue was measured using a 100 mm VAS⁽¹²⁾. Patients' weight and height were recorded to calculate patients' Body Mass Index (BMI). Underweight was defined in case of BMI <18.5, normal weight 18.5-24.9, over weight 25-29.9 and obesity if BMI ≥ 30 ⁽¹³⁾. Chest high resolution computed tomography scan (HRCT) was done using both techniques GE light speed plus MSCT 4 channels set. HRCT films were done in supine position with full inspiration without contrast enhancement. Image analysis was done by both the radiologist and chest consultant with inter-observer agreement. To assess the presence of rheumatoid interstitial lung disease.

Ethical approval and written informed consent:

An approval of the study was obtained from Ain Shams University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Statistical methodology: Recorded data were analyzed using the statistical package for social sciences, version 20 (SPSS Inc., Chicago, Illinois, USA). The comparison between two groups regarding quantitative data with parametric distribution was done by using one-way analysis of variance (ANOVA) when comparing between more than two means. Chi-square (X^2) test of significance was used in order to compare proportions between qualitative parameters. Binary logistic regression was used to predict the BMI of categorical variable based on one or more predictor variables. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant when $P \leq 0.05$, Significant.

RESULTS

The studied 200 patients were 172 (86%) females and 28 (14%) males. They had a mean age of 45.1 ± 14.2 years and a mean disease duration 7.042 ± 1.88 years. Clinical manifestation, disease activity, drugs received and laboratory investigations (Tables 1, 2).

Table (1): Demographic, laboratory investigations

Age (years)	Mean \pm SD	45.1 \pm 14.2
Sex	Number	%
Male		28 - 14%
Female		172- 86%
Disease duration (years)	Mean \pm SD	7.042 \pm 1.88
BMI	Mean \pm SD	31.7 \pm 6.34
Under-weight		26-13%
Normal BMI	Number-%	40-20%
Overweight		64-32%
Obese		70-35%
Hb (g/dL)	Mean \pm SD	12.07 \pm 1.44
TLC	Mean \pm SD	7.514 \pm 1.375
PLT count (mcL)	Mean \pm SD	292.07 \pm 7.06
ESR (mm/hr)	Mean \pm SD	40.95 \pm 2.35
CRP (mg/L)	Mean \pm SD	18.42 \pm 4.06
ALT (U/L)	Mean \pm SD	12.20 \pm 3.2
Sr.Cr (mg/dL)	Mean \pm SD	1.1 \pm 0.04
Total cholesterol (mg/dL)	Mean \pm SD	166.52 \pm 7.53
TG (ng/mL)	Mean \pm SD	101.6 \pm 14.5
LDL (mg/dL)	Mean \pm SD	91.30 \pm 13.1
HDL (mg/dL)	Mean \pm SD	57.4 \pm 10
RF positive	Number %	160 - 80%
Anti CCP positive (u/mL)	Number %	104 - 52%
DAS 28	Mean \pm SD	4.2 \pm 1.18
Remission	Number %	16 - 8%
Low	Number %	28 - 14%
Moderate	Number %	100 - 50%
High	Number %	56 - 28%

Table (2): Clinical and drug history

Parameter	N.-%
Arthritis	110-55%
Deformity	65-32.5%
Rheumatoid nodules	40-20%
Pleural effusion	50-25%
ILD	120-60%
Dry eye	74-37%
Dry mouth	62-31%
Skin vasculitis	10-5%
Corticosteroid	148-74%
Methotrexate	92- 46%
Hydroxychloroquine	168 -84%
Lefluonamide	96 -48%
Salazopyrine	16 – 8%
Biologic	10-5%

According to patients BMI, 70 patients were obese, 64 were overweight, 26 were underweight and 40 patients had normal BMI. Overweight and obese patients were significantly older in age, had longer disease duration ($P < 0.001$) with significantly female predominance ($P < 0.05$), had higher ESR, CRP, total cholesterol level, higher prevalence of RF and anti-CCP seropositivity ($P < 0.001$), higher DAS, HAQ and VAS score ($P < 0.001$) (Table 3).

Table (3): Comparison between 4 groups regarding demographic and laboratory data

	Underweight (n=26)	Normal BMI (n=40)	Over weight (n=64)	Obese (n=70)	Sig.
Age (years)	20±3.5	22.2±13.4	35.5±14.2	44.2±11.2	<0.001**
Disease duration	3.39±3.34	4.571±2.533	7.373±6.090	8.729±6.494	<0.001**
Sex					
Female	20 (76.9%)	33 (82.5%)	56 (87.5%)	63 (90.0%)	0.057
Males	6 (23.1%)	7 (17.5%)	8 (12.5%)	7 (10.0%)	
TLC	6.851±1.425	7.131±0.42	7.324±1.12	6.921±1.31	0.127
PLT (mcL)	192.341±6.71	183±7.52	324±6.12	321±32.1	<0.001**
ESR (mm/hr)	15±3.42	18±2.2	35.62±2.24	40.75±2.34	<0.001**
CRP (mg/L)	5.2±1.2	6.4±1.1	18.2±4.6	19.4±4.2	<0.001**
ALT (U/L)	11.23±2.1	11.32±2.4	11.42±1.1	12.02±2.2	0.239
Sr.Cr (mg/dL)	1.1±0.03	1.2±0.02	1.15±0.21	1.09±0.22	0.079
RF (160 pt)	6 (23.1%)	24 (60%)	60 (93.8%)	70 (100%)	<0.001**
Anti-CCP(104pt) (u/mL)	5 (19.2%)	11 (27.5%)	33 (51.6%)	55 (78.6%)	<0.001**
Total Cholesterol (mg/dL)	143±5	166±15.3	255±22.2	232±32	<0.001**
LDL (mg/dL)	78.21±2.1	72±2.4	80±10	77±13.6	0.062
HDL (mg/dL)	57.4±11.3	55±12.3	53.3±11.2	52±10.3	0.166
TG (ng/mL)	85.2±12.1	88.15±21	92.01±14	90.6±13	0.221
Number-% of patients					
Remission(16 PT)	9 (34.6%)	4 (10.0%)	2 (3.1%)	1 (1.4%)	<0.001**
Low disease activity (28 pt)	10 (38.5%)	10 (25.0%)	5 (7.8%)	3 (4.3%)	<0.001**
Moderate(100)	4 (15.4%)	16 (40.0%)	38 (59.4%)	42 (60.0%)	0.003*
High(56)	3 (11.5%)	10 (25.0%)	19 (29.7%)	24 (34.3%)	<0.001**
VAS	4.750±3.151	5.571±1.342	5.860±1.885	7.000±2.073	<0.001**
HAQ	0.750±0.681	0.986±0.866	1.160±0.721	1.778±0.756	<0.001**

Using: One Way Analysis of Variance; Chi-square test p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

Overweight and obese patients had more frequent arthritis, joint deformity ($P < 0.001$), higher prevalence of rheumatoid nodules ($P = 0.007$), pleural effusion ($P = 0.005$), RA-ILD ($P < 0.001$), frequent corticosteroid and methotrexate intake ($P < 0.001$) and frequent biologic drugs administration ($P = 0.018$) (Table 4).

Table (4): Comparison between 4 groups regarding clinical manifestations and drug history

Number -% of patients	Underweight (n=26)	Normal BMI (n=40)	Over weight (n=64)	Obese (n=70)	Sig
Arthritis(110)	2 (7.7%)	12 (30.0%)	36 (56.3%)	60 (85.7%)	<0.001**
Deformity(65)	4 (15.4%)	9 (22.5%)	15 (23.4%)	37 (52.9%)	<0.001**
Rheumatoid nodules(40)	0 (0.0%)	5 (12.5%)	11 (17.2%)	24 (34.3%)	0.007*
Skin vasculitic rash (10)	0 (0.0%)	2 (5.0%)	5 (7.8%)	3 (4.3%)	0.374
Dry eye (74)	10 (38.5%)	15 (37.5%)	22 (34.4%)	27 (38.6%)	0.962
Dry mouth (62)	9 (34.6%)	11 (27.5%)	18 (28.1%)	24 (34.3%)	0.804
Pleural effusion(50)	1 (3.8%)	5 (12.5%)	16 (25.0%)	28 (40.0%)	0.005*
ILD (120)	4 (15.4%)	10 (25.0%)	42 (65.6%)	64 (91.4%)	<0.001**
Corticosteroid (148)	8 (30.8%)	21 (52.5%)	51 (79.7%)	68 (97.1%)	<0.001**
Methotrexate(92)	3 (11.5%)	10 (25.0%)	31 (48.4%)	48 (68.6%)	<0.001**
HCQ(168)	23 (88.5%)	31 (77.5%)	54 (84.4%)	60 (85.7%)	0.614
Leflunomide(96)	8 (30.8%)	19 (47.5%)	30 (46.9%)	39 (55.7%)	0.187
Salazopyrin(16)	1 (3.8%)	5 (12.5%)	6 (9.4%)	4 (5.7%)	0.499
Biologic(10)	0 (0.0%)	0 (0.0%)	2 (3.1%)	8 (11.4%)	0.018*

Using: Chi-square test p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

Logistic regression analysis revealed that BMI have a significant effect on ESR, RF, anti-CCP, moderate and high disease activity, VAS and HAQ score (Table 5).

Table (5): Logistic regression analysis of BMI affecting on parameters in patients group

Parameters	B	Sig.	Exp(B)	95% C.I.	
				Lower	Upper
Age (years)	0.216	0.121	1.126	1.099	1.154
PLT (mcL)	0.518	0.245	3.286	0.997	6.658
ESR (mm/hr)	2.165	0.036	1.053	1.003	3.106
CRP (mg/L)	1.151	0.018	2.339	0.137	5.842
RF	0.187	0.026	3.438	1.566	9.332
Anti-CCP (u/mL)	1.382	0.019	1.078	0.998	1.164
T. Cholesterol (mg/dL)	0.196	0.319	0.124	0.999	1.049
Moderate activity	2.382	0.013	1.390	1.039	1.859
High activity	1.266	0.019	4.560	2.411	12.807
VAS	0.206	0.014	1.104	1.017	1.199
HAQ	1.520	0.014	2.748	0.729	7.766

This table showed that BMI have a significant effect on the ESR, CRP, RF, anti-CCP, moderate activity, high activity, VAS and HAQ, while age, PLT and T. cholesterol were insignificant.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory connective tissue disease which may cause joint destruction and functional disability⁽¹⁾ several parameters may be involved in poor disease outcome and high disease activity⁽⁷⁾.

This work aimed to study the prevalence of obesity among cohort of Egyptian RA patients and asses its relation to disease activity and extra-articular manifestation. In the current study, patients mean age was 45.1 ± 14.2 years. 86% of the patients were females and 14% were males. The high prevalence of RA among females may be attributed to genetic effect (x-linked) and role of hormonal effects⁽¹⁴⁾.

Based on patients BMI, 32% of the patients were overweight and 35% were obese. These results is nearly

similar to **Guimaraes et al.**⁽¹⁵⁾ study who reported that 26.9% of their patients were obese. Moreover, **Yacoub et al.**⁽¹⁶⁾ demonstrated that 30% of their patients were overweight and 16.8% were obese. Increased incidence of overweight in RA patients may be explained by reduced physical activity and long-term treatment of corticosteroid⁽¹⁾.

On comparing our RA patients after their classification according to BMI, we observed that overweight and obese patients were significantly older in age, had longer disease duration with statistically significant female predominance compared to underweight and patients with normal BMI. **Younis and AL-Bustany**⁽²⁾ reported that 42.1% of their obese RA patients' aged from 59-71 years, 48.6% their disease duration were more than 5 years and 51% of

them were females. These results are in disagreement to **Gharbia et al.**⁽¹²⁾ who concluded that there was no significant statistical difference between RA patients with normal BMI and overweight RA patients regarding age, disease duration and sex distribution.

Regarding laboratory parameters, our overweight and obese patients had highly significant increase in mean ESR, CRP and higher platelet count. This is in agreement with **Ellabban et al.**⁽¹⁸⁾ who reported that ESR and CRP were significantly higher among obese RA patients compared to non-obese. Besides, **Stavropoulos-Kalinoglou et al.**⁽¹⁹⁾ conducted a study on 294 RA patients and observed that there was higher CRP level among obese RA patients. In contrary to these findings, **Younis and AL- Bustany**⁽¹²⁾ did not find significant higher levels of ESR nor CRP among obese RA patients and they attributed high DAS28 score among those patients to the high number of tender and swollen joint count.

Our study showed that obese and overweight patients had significantly higher serum cholesterol level compared to underweight and those with normal BMI, however we did not detect significant difference regarding other lipid profile parameters. This is in harmony with **Ellabban et al.**⁽¹⁸⁾ who observed higher total cholesterol and TG level among obese RA patients.

RF and Anti-CCP sero-positivity are usually associated with more severe joint destruction and extra-articular manifestation⁽²⁰⁾. Indeed, **Gilesetal et al.**⁽²¹⁾ identified protective effect of obesity only in RA patients who were seropositive for RF and anti-CCP. This study revealed statistically significant higher prevalence of RF and anti-CCP seropositivity among overweight and obese patients. These results run in agreement with **Yacoub et al.**⁽¹⁶⁾ who observed higher level of RF and anti-CCP among obese RA patients. Moreover, **Ellabban et al.**⁽¹⁸⁾ reported nearly similar results.

On assessing disease activity in RA patients, we documented a significant increase in DAS 28, VAS and HAQ scores in overweight and obese patients compared to those with normal BMI or underweight. These data are in agreement with **Levitsky et al.**⁽⁹⁾ who reported that obesity was the strongest independent factor predicting non-remission among rheumatoid arthritis patients despite initiation of treatment with a target approach. Also, in a study conducted by **Ajeganova et al.**⁽¹⁴⁾, which enrolled 1596 patients with early RA. They concluded that obesity early and during follow up of RA patients was strongly related to high RA activity and more pain. Additionally, in a study conducted by **Sandberg et al.**⁽²²⁾, they concluded that overweight decreases the chance of achieving good disease control in RA patients receiving DMARDs. However, in contrary to these results, **Abuhelwa et al.**⁽¹⁾ reported that there was no significant association

between disease remission and over-weight. Furthermore, patients who were underweight tend to have lower remission rate compared to normal BMI patients. In addition, **Gharbia et al.**⁽¹⁷⁾ observed that normal weight and over-weight patients had significantly lower DAS28 score and HAQ score than obese ones.

Relationship between inflammation and obesity may be attributed to multiple factors. Free fatty acid, which are increased in case of excess adipose tissue, can activate macrophage and excess production of adiponectin. Besides, white adipose tissues produce TNF-alpha and IL-6. All these factors reveal the link between obesity and disease activity in RA patients⁽⁹⁾.

Regarding medication history, higher percentages of obese and overweight RA patients were on steroid, methotrexate and biological therapy compared to those patients with normal BMI and underweight, which may be attributed to the higher disease activity in those patients and strong need to powerful immunosuppression to control disease activity. However, **Gharbia et al.**⁽¹⁷⁾ and **Yacoub et al.**⁽¹⁶⁾ reported no difference between obese and normal BMI patients regarding drug intake.

In this study regarding RA clinical manifestations; arthritis, joint deformity and rheumatoid nodules were significantly more prevalent among obese and over-weight RA patients.

Pulmonary involvement in the form of presence of pleural effusion or interstitial pulmonary fibrosis (IPF), they were significantly more frequent among obese and over-weight RA individuals compared to those who were under weight or with normal BMI. This is in agreement with **Kronzer et al.**⁽²³⁾ who reported that obesity is a strong predictor for development of RA-ILD. However, **Yacoub et al.**⁽¹⁶⁾ reported that there were no statistically significant differences in BMI according to extra-articular manifestations.

Logistic regression analysis showed that BMI had a significant effect on the ESR, CRP, RF, anti-CCP, moderate activity, high activity, VAS and HAQ. While age, PLT and T. cholesterol were insignificant.

CONCLUSION

Overweight and obesity were frequent among Egyptian RA patients. It was associated with high disease activity and extra-articular manifestations. In turn, patients' weight reduction can help in improvement of patients' outcome and disease activity control.

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