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Impact of Body Mass Index on activity and therapeutic response in rheumatoid arthritis (about 80 cases).

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Abstract:

Introduction:

Obesity is a condition of chronic low-grade inflammation that induces several diseases. It has harmful consequences for health that go far beyond the scope of vascular risk factors. Its role in rheumatoid arthritis (RA) could be explained by the presence of numerous inflammatory cytokines in adipose tissue, including TNF alpha. The aim of this study was to assess body mass index (BMI) in patients with RA and determine its impact on disease activity.

Patients and methods:

An observational cross-sectional study was conducted in the rheumatology department between April 2018 and March 2019. It included patients followed for RA. Weight and height were reported, and BMI was assessed according to the WHO classification: thinness <18.5kg/m², normal build: 18.5 - 24.9kg/m², overweight: 25 - 29.9kg/m², and obesity≥30kg/m². We compared clinical and biological characteristics, disease activity score (DAS28), functional impact (Health Assessment Questionnaire (HAQ)), and therapeutic response.

Results:

80 patients were included, 93% women and 7% men, with a sex ratio of 0.5. The average age was 52.64 years ± 10.74 [22 - 81], and the average BMI was 26.91kg/m². Among patients, 49% were overweight, 22% were obese, 26% were of normal weight, and 3% were thin. The mean DAS28 was 5.31 ± 1.49. Mean DAS28 scores decreased with BMI from thinness (4.45 ± 1.4), normal (4.22 ± 1.2), overweight (3.45 ± 1.2), and obesity (2.90 ± 1.5). Analysis of variance (ANOVA) did not detect a statistically significant relationship between different categories of BMI, DAS28, and therapeutic response; however, rheumatoid factor was more severe in lean patients with a p-value of 0.01.

Conclusion:

Despite the limitations of this study, including its limited timeframe and small sample size, the findings suggest that body mass index (BMI) does not appear to have an impact on disease activity as assessed by the DAS28 in patients with rheumatoid arthritis (RA).Further exploration could help identify additional potential factors influencing RA activity and guide clinical management strategies for this patient population.

Keywords: Rheumatoid arthritis, BMI, DAS28.

1. Introduction :

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatic condition, affecting 0.5 to 1% of individuals in the general population. It predominantly afflicts women (with a ratio of 3 to 1) between the ages of 40 and 60 years. RA is a multifactorial chronic inflammatory disease characterized by relapses and remissions of varying duration. It involves chronic inflammation of the synovial membrane, leading to osseocartilaginous destruction. As an autoimmune disease, RA presents with extra-articular systemic manifestations, positivity for rheumatoid factor (RF), and citrullinated antipeptide antibodies (ACPA).

As the etiology of RA remains unknown, various hypotheses suggest the involvement of immunological factors on a favorable genetic background, as well as the influence of hormonal and environmental factors in disease onset and progression. RA can result in significant disability, leading to psychological, social, and professional consequences. Moreover, RA is associated with changes in body composition, characterized by low muscle mass (cachexia) and excess body fat [1]. Compared to the general population, RA patients have lower muscle mass and higher fat content.

Adipose tissue is now recognized as an active site that exerts endocrine and immune effects on several organs through the release of adipocytokines [2]. These factors include leptin, resistin, adiponectin, visfatin, as well as classical cytokines such as tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), IL-6, and monocyte chemotactic protein 1 (MCP-1), which are expressed by inflammatory cells infiltrating adipose tissue.

These molecules influence immune functions and can contribute to the development of several diseases, including diabetes mellitus, atherosclerosis, RA, and osteoarthritis [3-4]. While the actions of various cytokines in RA, an immune-mediated chronic inflammatory disease primarily affecting the joints, are well-documented [5], the role of adipose tissue remains controversial. Overweight is characterized by a BMI $\geq$ 25 kg/m², with obesity defined as a BMI $\geq$ 30 kg/m². The objective of this study was to assess BMI in patients with RA and determine its impact on disease activity and therapeutic response.

2. Patients and methods :

a. Patients:

- This is a retrospective cross-sectional observational study of patients with RA conducted within the rheumatology department between April 2018 and March 2019.

- ***Inclusion criteria:*** Any patient with RA diagnosed according to the ACR (American College of Rheumatology) 1987 criteria or ACR/EULAR 2010 criteria (European League Against Rheumatism) was included. Inclusion occurred either during hospitalization in the rheumatology department or during an outpatient consultation.
- ***Exclusion criteria:*** Patients ≤ 16 years old were excluded, as were patients with concomitant inflammatory diseases, malignant tumors, central nervous system diseases, chronic kidney and liver diseases, and thyroid diseases in addition to RA. Pregnant women with RA were also not included.

b. Methods :

All collected data were recorded on a standardized form, including the following sections:

- ***Sociodemographic data:*** These included age, sex, and medical history (diabetes, arterial hypertension, dyslipidemia, smoking, etc.). BMI was calculated using the classic formula: weight in kilograms divided by height in square meters (Kg/m^2). The WHO defines overweight and obesity as follows: overweight when the BMI is ≥ 25, and obesity when the BMI is ≥ 30.
- ***Clinical characteristics of RA:*** This section analyzed the onset age of RA, time to diagnosis, time to treatment initiation, and disease duration. It also assessed the deforming and/or erosive nature of RA and the presence of extra-articular manifestations.
- ***Paraclinical characteristics of RA:***
    - ***Biological assessment:*** Inflammatory markers (sedimentation rate (ESR) and C-reactive protein (CRP)) and immunological markers (rheumatoid factor (RF) and citrullinated antipeptide antibodies (ACPA)) were examined.
    - ***Radiological assessment:*** Standard x-rays of the hands, feet, chest, and pelvis were conducted to detect typical RA signs. Osteoarticular ultrasound was performed for some patients to detect subclinical synovitis and infradiological erosions.
- ***RA assessment:*** Disease activity was evaluated using the Disease Activity Score (DAS 28). RA was classified as "remission" if DAS 28 was <2.6, "low activity" if ≤ 3.2 and > 2.6, "active" if DAS 28 > 3.2, "moderately active" if > 3.2 and ≤ 5.1, and "very active" if > 5.1. Functional disability was assessed using the HAQ (Health Assessment Questionnaire).
- ***Therapeutic characteristics:*** The treatment received by each RA patient was specified. The impact of BMI on methotrexate (MTX) treatment efficacy was evaluated using biological inflammatory markers (CRP, ESR) and DAS 28 at baseline, 3 months, and 6 months. Therapeutic response was measured by Δ DAS 28, which

represents the difference between initial and subsequent DAS 28 scores.

c. Statistical analysis:

Data were entered and coded in Excel and analyzed using SPSS v20 software in collaboration with the epidemiology unit of the Faculty of Medicine and Pharmacy. Descriptive analysis of the population and collected data was conducted. Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were expressed as numbers and percentages. Bivariate analysis was performed, including ANOVA analysis for quantitative variables and the chi-square test for qualitative variables. A p-value <0.05 was considered statistically significant.

3. Results:

In our study, patients with a BMI <18.5 exhibited an early onset of rheumatoid arthritis (RA) with a mean age of 35 ± 35.35 years compared to other BMI groups; however, this association was not statistically significant ($p = 0.822$). The mean duration of RA was longer in patients with a normal BMI (11.23 ± 5.78 years) compared to other groups, although these results did not reach statistical significance ($p = 0.386$). Regarding deformities and extra-articular manifestations, such as rheumatoid skin nodules, Gougerot Sjögren syndrome, kidney, and eye involvement, they were associated with obesity, but the associations were not statistically significant with p-values of $p = 0.380$, $p = 0.141$, $p = 0.430$, $p = 0.330$, and $p = 0.487$, respectively.

None of the parameters, including inflammatory and immunologic markers, showed statistically significant associations with BMI. In our patient cohort, there was no significant association between RA activity as assessed by the baseline DAS28CRP score and BMI ($p = 0.629$). RA severity was observed in 50% of overweight patients compared to other BMI groups, but this finding did not reach statistical significance ($p = 0.282$).

In our study, we did not find a significant association between conventional disease-modifying antirheumatic drugs (DMARDs) and BMI. Moreover, the biological inflammatory syndrome was markedly reduced at 3 months and 6 months in all BMI groups, suggesting a potential therapeutic response irrespective of BMI status.

Commentary:

The findings of our study provide valuable insights into the relationship between BMI and various clinical parameters in patients with rheumatoid arthritis (RA). Despite observing trends in certain associations, such as earlier onset of RA in patients with lower BMI and a longer duration of RA in those with normal BMI, our study did not yield statistically significant results in these regards. Similarly, while obesity appeared to be associated

with certain extra-articular manifestations of RA, the associations did not reach statistical significance.

Our study underscores the complex nature of RA pathogenesis and the multifactorial influences contributing to disease progression and severity. Although adiposity and its associated inflammatory milieu have been implicated in various chronic diseases, including RA, our findings suggest that BMI alone may not be a decisive factor in determining disease activity or severity in RA patients.

Furthermore, the lack of significant associations between conventional DMARDs and BMI highlights the need for further investigation into the interplay between therapeutic interventions and metabolic factors in RA management. The observed reduction in biological inflammatory markers across all BMI groups following treatment indicates a potential universal response to therapy, irrespective of BMI status, which warrants exploration in future studies.

Overall, our study contributes to the growing body of literature aimed at elucidating the complex mechanisms underlying RA pathophysiology and treatment response, thereby informing more personalized approaches to patient care and management strategies.

Table 1 : Characteristics of sample according to BMI.

Variables		BMI				p
		Thinness (N= 2)	Normal weight (N=21)	Overweight (N=39)	Obesity (N=18)	
Average age of onset (years)		35 ± 35,35	40,61 ±13,76	39,15 ± 13,48	42,11 ±10,38	0,822
Average development time (years)		3,50 ± 0,70	11,23 ± 5,78	9,61 ± 7,36	9,33 ± 5,04	0,386
Deformations (%)		4,1	28,6	46,9	20,4	0,380
Extra-articular manifestations (%)	**Cutaneous rheumatoid nodule**	0	0	25	75	0,141
	Sd de Gougerot Sjögren	0	25	25	50	0,430
	Kidney damage	0	0	0	100	0,330
	Pulmonary involvement	14,3	14,3	71,4	0	0,056
	Ocular involvement	0	0	0	100	0,487

Table 2: Association analysis of various biological parameters collected in our population and BMI.

Variables		BMI				p
		Thinness (N= 2)	Normal weight (N=21)	Overweight (N=39)	Obesity (N=18)	
FR positive	N	1	18	31	14	0,929
	%	1,6	28,1	48,4	21,9	
ACPA positive	N	0	12	18	8	0,324
	%	0	31,6	47,4	21,1	
Initial VS (mmH1)		29,50± 16,20	34,35 ± 24,71	32,08 ±18,17	34,80±24,64	0,289
CRP (mg/l)		16,05± 14,30	24,24 ± 24,38	33,20 ± 17,20	32,10±18,81	0,145
DAS28CRP initial		6,10 ± 1,80	5,35 ± 1,40	5,28 ± 0,80	6,40 ±0,94	0,629
RA severity (%)		1,4	26,4	50	22,2	0,282

4. Discussion :

Rheumatoid arthritis (RA) is a multifactorial chronic inflammatory disease with an estimated frequency of occurrence of 0.5 to 1% in the general population, with a predominance among women. It evolves through relapses interspersed with remissions of variable duration and is characterized by chronic inflammation of the synovial membrane, leading to osseocartilaginous destruction. The natural progression of RA often leads to joint deformities and erosions, resulting in varying degrees of functional impairment that can significantly impact patients' quality of life and life expectancy.

The etiology of RA remains unknown, although several factors are implicated in its induction and/or exacerbation. Genetic predisposition, particularly involving genes of the major histocompatibility complex type II, particularly the HLA-DRB1 locus, is strongly implicated. Environmental and hormonal factors, such as stress, tobacco use, infections, among others, also play roles in disease onset.

RA is classified as an autoimmune and systemic disease due to the presence of extra-articular systemic manifestations and autoantibodies, mainly rheumatoid factor (RF) and citrullinated antipeptide antibodies (ACPA). Its

immunological mechanism involves both innate and acquired immunities, with toll-like receptors, cytokines, and complement pathways contributing to an intense inflammatory reaction affecting the synovium.

Changes in body weight among RA patients present a complex scenario. Active disease can lead to weight loss and rheumatoid cachexia, while adipose tissue, acting as an active site, releases adipocytokines with immunological effects.

The association between body mass index (BMI) and the clinical course of RA remains debated, with evidence suggesting a relationship between inflammation and obesity. Excess production of adipocytokines, especially in obese individuals, perpetuates chronic inflammation.

Our study found that 71% of RA patients were overweight or obese (49% and 22% respectively), which differs from the rates reported in the literature series [8, 9]. However, we found no significant association between BMI and baseline DAS28CRP scores, consistent with previous studies [10].

The exact mechanism by which BMI influences disease activity remains unclear but is likely related to levels of pro-inflammatory cytokines and adipokines. While some studies have shown a positive association between obesity and disease activity [7, 16], others have reported conflicting results regarding the impact of BMI on therapeutic response.

Recent studies have suggested that higher BMI may be associated with a poorer response to methotrexate [15,16] and other treatments, with obesity representing a significant independent factor for predicting non-remission and lower response rates to treatment in RA patients [13,17,18,19].

In conclusion, the relationship between BMI and RA remains complex and warrants further investigation to elucidate the underlying mechanisms and optimize therapeutic strategies for patients with RA, particularly those who are overweight or obese.

5. Conclusion :

Despite the limitations of this study, including its limited sample size and potential confounding factors, our findings suggest that body mass index (BMI) may not significantly impact disease activity as assessed by DAS28 score and methotrexate response as assessed by delta DAS in patients with rheumatoid arthritis (RA). However, further research examining the relationship between BMI and clinical response to biologics, while

considering the diverse mechanisms underlying RA pathogenesis, is warranted in larger study populations. This may provide deeper insights into the interplay between BMI and treatment outcomes in RA patients, ultimately guiding more effective therapeutic strategies.

Conflict of interest statement: The authors have declared that no competing interests exist for this work.

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