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Are obesity and rheumatoid arthritis interrelated?

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Summary

Objectives: In recent years, both the prevalence of obesity and the incidence of RA have been rising. Our aim was to assess the association between overweight or obesity and rheumatoid arthritis (RA).

Design: Patients who were diagnosed with RA were compared with population-based controls, matched for age and sex (by a ratio of 1:5). Body measurements and smoking status were collected from medical records. Body mass index was classified in WHO categories of underweight, normal, overweight and obese (<18.5, 18.5-<25, 25-<30, ≥30 kg/m²). χ^2 and t-tests and logistic regression models were used to compare the study groups and to assess the association between obesity and RA.

Setting: A cross-sectional analysis performed utilizing the database of Clalit Health Services, the largest healthcare provider organisation in Israel. Data were collected from the beginning of computerised database usage (around year 2000) until 2015.

Participants: CHS covers over 4.4 million enrollees, of which all RA patients and matched controls were selected.

Main outcome measures: Proportion of obesity (BMI ≥ 30.0 kg/m²) among RA patients and controls.

Results: The study included 11 406 patients with RA and 54 701 controls. The proportion of obese subjects among RA patients was higher in comparison with controls, (33.4% vs 31.6%, respectively). In multivariate regression model, smoking and obesity were found to be associated with RA, whereas male gender was found as inversely related to RA.

Conclusions: Our findings demonstrate that obesity is significantly associated with RA. This finding underlines the role that obesity plays in inflammation and autoimmune conditions.

1 | INTRODUCTION

Obesity remains a major health issue affecting as many as two-thirds of adults in the USA and one-third of American children.¹ Obesity is turning into a substantial public health crisis worldwide; its prevalence is rapidly increasing in numerous industrialised countries. Moreover, the changing patterns of nutrition and activity, as well as the increasing consumption of fast food, have triggered obesity to hit developing

countries as well. Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer.²⁻⁵

The linkage between obesity and RA is being investigated today from few different aspects. It has been previously shown that obesity raises RA activity and comorbidities alike (cardiovascular disease, type 2 diabetes, chronic pulmonary disease), while decreases the quality of life of RA patients as well as the remission rates of the disease.⁶⁻¹⁰

Arnon Cohen and Howard Amital share equal contribution for this article.

However, paradoxically, it has been shown that obesity protects from radiographic joint damage.¹¹ Several studies have examined the potential influence of obesity on the development of RA with inconsistent results. Recently, Lu et al¹² published the largest prospective study investigating this issue; they followed more than 200 000 women enrolled in Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII). In both cohorts, women completed an initial questionnaire and have been followed biennially to update exposures, lifestyle, health practices and disease diagnoses. The authors detected a trend towards increased risk of all RA among overweight and obese women. They also demonstrated that 10 cumulative years of being obese increased the risk of RA at younger ages by 37%.

The underlying hypothesis is that the increased inflammation associated with obesity contributes to the risk and severity of RA. The role of white adipose tissue in modulating immunity and inflammation, in addition of its role as an energy storage under conditions of caloric surplus, demonstrates its importance as an active participant in regulating physiologic and pathologic processes.¹³ Adipose tissue produces and secretes a variety of pro-inflammatory and anti-inflammatory factors, including the adipokines leptin, adiponectin, resistin and visfatin as well as cytokines and chemokines, including TNF- α , IL-6, monocyte chemoattractant protein 1 and others.¹⁴⁻¹⁶

The goal of our study was to investigate the linkage between RA and BMI using the large medical database of the Clalit Health Services (CHS), the largest health maintenance organisation (HMO) in Israel.

2 | METHODS

The study was designed as a cross-sectional analysis utilising the Clalit Health Services (CHS) database. The CHS is the largest managed care organisation in Israel, serving a population of approximately 4 400 000 enrollees. The CHS have a comprehensive database with continuous real-time input from pharmacies, medical care facilities and administrative systems. Patients were defined as having RA when there was at least one documented diagnosis of RA in the medical records registered by a community physician or when RA was listed in the diagnoses of discharge letters from a hospital. For each RA patient, five controls without RA were randomly selected from CHS database and matched by age and sex.

Data derived from the CHS database included age, sex, socioeconomic status (SES), body mass index (BMI) and smoking status. SES was defined according to the poverty index of the member's residence area as defined during the national census. More specifically, the poverty index was computed based on several parameters, including household income, education, crowding, material conditions and car ownership, among others. It ranged from 1 to 20, based on cluster analysis, with 1 as the lowest SES and 20 as the highest. We divided the population into 3 categories according to their SES. Body mass index was classified according to the WHO categories of underweight, normal, overweight and obese (<18.5, 18.5-<25, 25.0-<30, \geq 30.0 kg/m²). Data were collected from the beginning of computerized database usage (around year 2000) until 2015.

What was known

- Obesity and inflammation are tightly associated
- Higher circulating inflammatory cytokines have been reported in obese subjects
- Obese patients with rheumatoid arthritis have higher rates of various extra-articular comorbidities

What is new

- The present study has underlined that in a "real life" population insured by the largest health maintenance organisation in Israel, obesity was independently associated with the coexistence of rheumatoid arthritis

2.1 | Statistical analysis

The distribution of sociodemographic and clinical factors was compared between patients with and without RA using χ^2 test for categorical variables (sex, socioeconomic status, comorbid diseases) and a Student's *t*-test continuous variables for age. Odds ratios (OR) across strata were calculated with 95% confidence interval. A logistic regression model was used to estimate the association between RA and obesity. Statistical analysis was performed using R Statistical Software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the Institutional Review Board of the Soroka Medical Center, Israel (approval no. 10044), and was exempted from the need to sign an informed consent form. The Declaration of Helsinki protocols were followed.

3 | RESULTS

The study included 11 406 patients with RA and 54 701 age- and sex-matched controls. Characteristics of the study population are presented in Table 1. The proportion of obesity in patients with RA was increased compared with the controls: 33.4% and 31.6%, respectively, $P < .001$. There was a significantly higher proportion of smokers among patients with RA as compared to controls (33.5% vs 29.7%, respectively). RA patients had increased odds being in a medium (but not high) SES as compared with controls. In a multivariate logistic regression analysis, obesity was found to be significantly associated with RA (OR 1.09, 95% CI 1.04-1.14). Smoking and obesity were also found to be independently associated with RA whereas male sex was found to be inversely related to RA while (Table 2).

4 | DISCUSSION

Obesity has reached epidemic proportions in many nations. Elevated body mass index, particularly caused by abdominal obesity, has been associated with a number of diseases and metabolic abnormalities, many of which have high morbidity and mortality.¹⁷ Over the last

TABLE 1 Descriptive characteristics of the study population (n = 66 107)

Characteristic	Control group N = 54701	RA group N = 11406	P-value
Age, y	62.2 (15.4)	62.2 (15.5)	.938
Female gender	42205 (77.2%)	8822 (77.3%)	-
Socioeconomic status			
Low	21279 (39.0%)	4349 (38.2%)	-
Medium	21613 (39.6%)	4673 (41.1%)	.015
High	11697 (21.4%)	2361 (20.7%)	.657
Smokers	16255 (29.7%)	3818 (33.5%)	<.001
BMI	28.1 (5.81)	28.3 (6.01)	<.001
Obese (BMI>30)	37410 (68.4%)	7598 (66.6%)	-
Non-obese (BMI<30)	17291 (31.6%)	3808 (33.4%)	<.001

RA, rheumatoid arthritis; BMI, body mass index, kg/m²; SD, standard deviation.

TABLE 2 Logistic regression for covariates associated with RA

Variable	Odds ratio	95% CI	P-value
Age, per year	1.00	1.00-1.00	.927
Male gender	0.94	0.90-0.99	.021
Socioeconomic status			
Medium vs Low	1.06	1.01-1.11	.021
High vs Low	0.99	0.94-1.05	.762
Smoking	1.21	1.15-1.26	<.001
Obesity (BMI>30)	1.09	1.04-1.14	<.001

CI, confidence interval.

several decades, there have been several studies addressing the association between RA and obesity and investigating the added risk derived from being obese compared with the general population.¹⁸⁻²⁰ The mechanism by which obesity may lead to RA is unidentified. However, there are numerous potential mechanisms to explain this condition; one possible mechanism is based on the association between obesity and chronic inflammation. The obese state is characterised by low-grade systemic inflammation, as indicated by increased levels of CRP and other inflammatory markers in the circulation of obese and overweight subjects.²¹⁻²³ Far beyond a mere inert lipid storage, the current view of adipose tissue is that of an active secretory organ, producing numerous bioactive molecules that regulate carbohydrate and lipid metabolism, immune function and blood coagulability, modulate appetite and may serve as blood markers of cardio metabolic risk. These mediators play a major role in the human body physiology and can have an effect on insulin resistance, metabolic syndrome and cardiovascular disease.^{24,25}

Given that ongoing inflammation marks many autoimmune diseases, chronic obesity presents a predisposed systemic environment to support the progression of autoimmune diseases. Altered systemic adipokines levels and/or local adipokines levels have been reported in a variety of autoimmune conditions.^{26,27} Increased expression of leptin has been associated with multiple autoimmune diseases.²⁷ Moreover,

leptin has emerged as an important regulator of inflammation, by acting as a pro-inflammatory mediator during both the innate and the adaptive immune response.²⁸

Several studies have shown that leptin-deficient mice have a reduced inflammatory response when rheumatoid-like disease was induced.^{29,30} Previous studies have also shown that adiponectin and resistin levels are elevated in the synovial fluids of patients with RA compared with that seen in patients with osteoarthritis and found a positive correlation between resistin and systemic markers of inflammation such as CRP.³¹

Another possible mechanism for the association between obesity and RA may derive from the prevalent occurrence of vitamin D deficiency among obese individuals. Vitamin D deficiency is known to be highly prevalent among individuals with different autoimmune disorders including RA.^{32,33}

An additional mechanism is based on the relationship between obesity and sex hormones. Obese men and women have higher serum levels of estrogens and androgens. Estrogen not only stimulates antibody (and autoantibody) production but also has a role in the breakdown of B-cell tolerance.³⁴⁻³⁶

Our study clearly validates this suggested association between RA and obesity. The results clearly point out that RA occurs more frequently among obese people. Nevertheless, since our study is cross-sectional, it is essential to deal with the question whether RA can lead to obesity. No data was found dealing with this question. Despite that, there are few mechanisms leading to weight gain in RA. Firstly, the joint pain can lead to immobility and consequent weight gain. Secondly, corticosteroids, a common treatment for RA, often ends up with weight gain. In this article, we focused on the role obesity may have as a risk factor for coexistent RA. The strength of this research arises mainly from the large sample size for both study and control groups. Moreover, the extensive demographic information from the CHS database, which included the entire population of the Clalit Medical Database, allowed for this comprehensive analysis. However, our study has several limitations. The study has an observational design and not an interventional one, which is an inherent limitation to

any cross-sectional study of this type. Previous experience with the CHS population-based study has indicated that the data are of high quality and that the associations that were detected were identical to those that were observed when smaller groups of patients with definite diagnoses were used.³⁷⁻⁴¹ Our study revealed statistically significant difference towards medium (but not high) SES among RA patients as compared with controls, but the difference was small and without an overt clinical impact.

In conclusion, this research underlines the significance of obesity as an independent factor associated with RA. A better understanding of the arthritis-obesity interaction will help us to improve a personalised management directed against both the disease and its associated comorbidities.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

Lior Dar, Shmuel Tiosano, Abdulla Watad and Nicola Luigi Bragazzi were involved in data analysis and manuscript preparation; Devi Zisman was involved in manuscript preparation; Doron Comaneshter was contributed towards data analysis; Arnon Cohen was involved in planning, data analysis and manuscript preparation; Howard Amital was involved in planning, data analysis, manuscript preparation and editing.

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