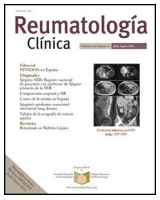
Reumatol Clin. 18 (2022) 531–537

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org



Original Article

Relationship between polyautoimmunity and sarcopenic obesity in rheumatoid arthritis patients☆

Natalia Mena-Vázquez,[a,b,*] Sara Manrique-Arija,[a,b,**] María Carmen Ordoñez-Cañizares,[a,b] Rocio Redondo-Rodriguez,[a,b] José Rioja Villodres,[a,c] Laura Cano-Garcia,[a,b] Francisco Javier Godoy-Navarrete,[a,b] Francisco Gabriel Jiménez Nuñez,[a,b] Gisela Diaz-Cordovés Rego,[a,b] Inmaculada Ureña Garnica,[a,b] Antonio Fernández-Nebro[a,b,c]

[a] *Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain*
[b] *UGC de Reumatología, Hospital Regional Universitario de Málaga, Málaga, Spain*
[c] *Departamento de Medicina y Dermatología, Centro de Investigaciones Médico-Sanitarias (CIMES), Universidad de Málaga, Málaga, Spain*

ARTICLE INFO

Article history:
Received 28 March 2021
Accepted 17 June 2021
Available online 8 December 2021

Keywords:
Rheumatoid arthritis
Polyautoimmunity
Sarcopenic
Obesity

ABSTRACT

Objective: Sarcopenia is a major cause of morbidity in rheumatoid arthritis patients. Our purpose was to determine whether polyautoimmunity is associated with sarcopenia and alterations in whole body composition in patients with rheumatoid arthritis (RA).
Methods: We performed a cross-sectional observational study of a series of cases of RA. All patients were recruited consecutively from a rheumatology clinic. Body composition by dual-energy x-ray absorptiometry (DEXA) was assessed. The variables of interest were polyautoimmunity (RA associated with other autoimmune diseases), sarcopenia, fat mass, and body mass index (BMI). Other variables included were clinical-analytical and inflammatory cytokines and adipokines. The relationship between sarcopenic obesity and the presence of polyautoimmunity was studied using multivariate analysis.
Results: Of the 94 patients with RA included in the study, 15 (16%) had polyautoimmunity. A total of 23 patients with RA (24.5%) had sarcopenia, which was more prevalent in patients with polyautoimmunity than in patients without polyautoimmunity (46.7% vs 20.3%; p = .029). Sarcopenia was not associated with body fat content (p = .870) or with BMI (p = .998). The multivariate analysis showed the factors associated with polyautoimmunity in RA to be sarcopenia (odds ratio [95% CI], 4.80 [1.49-13.95]), BMI (1.18 [1.04-1.35]), and resistin (1.249 [1.01-1.53]).
Conclusion: Sarcopenia and obesity were more prevalent in patients with RA and polyautoimmunity. Resistin values were also higher in this group than in patients with RA without polyautoimmunity.
© 2021 Published by Elsevier España, S.L.U.

Relación entre poliautoinmunidad y obesidad sarcopénica en pacientes con artritis reumatoide

Palabras clave:
Artritis reumatoide
Poliautoinmunidad
Sarcopenia
Obesidad

RESUMEN

Objetivo: Analizar si la poliautoinmunidad en los pacientes con artritis reumatoide (AR) se asocia con sarcopenia y alteraciones de la composición corporal total.
Métodos: Estudio observacional transversal de una serie de casos de pacientes con AR, reclutados consecutivamente de la consulta de reumatología. Se evaluó la composición corporal mediante absorciometria de rayos X de energia dual (DXA). Las variables de interés fueron la poliautoinmunidad (AR asociada a otras enfermedades autoinmunes), sarcopenia, masa grasa e índice de masa corporal. Otras variables

☆ Please cite this article as: Mena-Vázquez N, Manrique-Arija S, Ordoñez-Cañizares MC, Redondo-Rodriguez R, Rioja Villodres J, Cano-Garcia L, et al. Relación entre poliautoinmunidad y obesidad sarcopénica en pacientes con artritis reumatoide. Reumatol Clin. 2022;18:531–537.
* Corresponding author.
** Corresponding author.
E-mail addresses: nataliamenavazquez@gmail.com (N. Mena-Vázquez), sarama_82@hotmail.com (S. Manrique-Arija).

2173-5743/© 2021 Published by Elsevier España, S.L.U.

incluidas fueron clínico-analíticas y citoquinas inflamatorias y adipoquinas. La relación entre obesidad sarcopénica y la presencia de poliautoinmunidad se estudió mediante análisis multivariable.
Resultados: De los 94 pacientes con AR incluidos en el estudio, 15 (16%) tenían poliautoinmunidad. Un total de 23 (24,5%) pacientes con AR presentaron sarcopenia, la cual fue más prevalente en los pacientes con poliautoinmunidad en comparación con los demás (46,7 vs. 20,3%; p = 0,029). La sarcopenia no se asoció con el contenido corporal de grasa en la composición corporal (p = 0,870) ni con el índice de masa corporal (IMC) (p = 0,998). En el análisis multivariante, los factores asociados a la poliautoinmunidad en AR fueron la sarcopenia (odds ratio [IC 95%], 4,80 [1,49-13,95]), el IMC (1,18 [1,04-1,35]), y la resistina (1,249 [1,01-1,53]).
Conclusión: Los pacientes con AR con poliautoinmunidad mostraron una mayor prevalencia de sarcopenia y obesidad, además tuvieron valores más elevados de resistina en comparación con pacientes con AR sin poliautoinmunidad.

© 2021 Publicado por Elsevier España, S.L.U.

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease of unknown origin which mainly affects the joints, although it is also frequently systemic. Sarcopenia is a syndrome characterised by a progressive and generalised loss of skeletal muscle function and mass which is associated with a higher risk of falling, muscle weakness, physical disability, poor quality of life and mortality[1–4]. Although sarcopenia is a multifactorial, age-associated phenomenon, it may be observed in chronic inflammatory states associated with RA and with other systemic diseases[5,6]. Previous studies show that 20%-40% of patients with RA have a reduced lean mass, low muscle strength, sarcopenia and sarcopenic obesity according to the following diagnostic criteria: *The European Working Group on Sarcopenia in Older People* (EWGSOP)[1,4,5,7]. Among other factors that have been associated with sarcopenia in RA is the inflammatory activity and higher severity of the disease[4].

Polyautoimmunity is characterised by the presence of two or more well-defined autoimmune diseases (AIDs) in the same patient. This phenomenon has often been described in systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS) in approximately 40%[8] and in 15%-20% of patients with RA[9,10]. The medical presentation of diseases such as SLE or SS are often made worse and are associated with factors such as the female sex, joint involvement, anti-Ro antibody positivity and reduced hydroxychloroquine uptake[8,11]. The factors associated with polyautoimmunity in RA have been studied to a lesser extent[9,12]. Barragán-Martínez et al. observed an association of polyautoimmunity with abdominal obesity, but this was only so for the female sex[12]. In another recent study obesity was the only independent factor associated with polyautoimmunity in patients with RA, regardless of gender[10]. Also, in a systematic review on polyautoimmunity-associated factors in different AIDs, the female sex was associated with SLE, SS and systemic sclerosis polyautoimmunity, whilst cardiovascular disease and overweight was only associated with polyautoimmunity in RA[9].

The exact mechanism with which obesity is associated with polyautoimmunity in RA remains unknown, although possible explanations include imbalances in proinflammatory adipokines and cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6)[13], together with increased Th17[14] cell polarisation and increased macrophage apoptosis inhibitor[15]. The aim of our study was[1] to analyse whether polyautoimmunity in RA patients is associated with sarcopenia and alterations in total body composition[2] and whether the proinflammatory adipokine and cytokine profile could play a role.

Pacients and methods

Study design

We conducted a cross-sectional study of a case series of patients with RA. The study was conducted in the Instituto de Investigación Biomédica de Málaga (IBIMA) by the Rheumatology Department of the Hospital Regional Universitario de Málaga (HRUM) in Spain. The study was approved by the Clincial Research Ethics Committee (CREC) of HRUM (Code 112-N-19).

Sample

The patients were recruited consecutively between June 2017 and September 2019 from rheumatology outpatient units. Inclusion criteria were as follows: age ≥ 16 years; RA according to the 2010 ACR/EULAR criteria classification[16]. Patients were divided into two groups depending on the presence or absence of polyautoimmunity, and whether they met with the operational definitions.

Protocol

Patients with RA are usually followed-up and treated at a specific practice every three to six months in keeping with a prospective data collection protocol. All subjects were interviewed and explored by a rheumatologists on the date indicated for this study. Biological samples were collected after 12-16h fasting before 10:00 a.m. After this whole-body dual-energy X-ray absorptiometry (DXA) scanning was performed.

Variables and operational definitions

The main variable was polyautoimmunity and secondary variables included anthropometric measurements and whole-body DXA scanning body composition. Polyautoimmunity was defined when RA classification criteria were simultaneously met in keeping with ACR/EULAR 2010[16] and other autoimmune diseases (AIDS)[9,11,17,18]. The AIDs considered were as follows: rheumatic diseases (SLE, spondyloarthritis, inflammatory myopathy, systemic sclerosis, SS and antiphospholipid syndrome), skin diseases (alopecia areata, psoriasis and vitiligo), endocrine disorders (diabetes mellitus type 1, Addison's disease, Graves-Basedow disease and Hashimoto thyroiditis), digestive disorders (celiac disease, primary biliary cholangitis, ulcerative colitis, Crohn's disease, and autoimmune hepatitis), disorders of the nervous system (multiple sclerosis). Multiple autoimmune syndrome (MAS) was defined as

the concurrence of three of more autoimmune diseases in the same patient.

Anthropometric measurements included body mass index (BMI) calculated as body weight (kg/height [m^2]) and patients were classified as underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29,9) and obese (> 30), according to the World Health Organisation (WHO)[19], and using the criteria adapted for RA issued by Stavropoulos-Kalinoglou et al. as underweight (< 18), normal weight (18.0-22.9), overweight (23-27,9) and obese (> 28)[20], together with waist and hip circumference (cm), and waist to hip ratio[21].

Body composition was measured by DXA (GE Lunar Prodigy software CORETM 2006) and included total mass (kg), fat mass (g), lean mass (g) and measurement of lean and fat mass and android and gynoid fat. The fat mass index was defined as fat mass (kg)/squared height (m^2) and the fat-free mass index as the fat-free mass (kg)/squared height (m^2). The appendicular skeletal muscle mass (ASM) was calculated as the sum of the skeletal muscle mass on the arms and legs, on the assumption that all non fatty tissue and non bone tissue is skeletal muscle[22,23]. Sarcopenia was defined as a relative skeletal mass index (RSMI)<5.5 kg/m^2 for women and <7.26 kg/m^2 for men[4,22]. The RSMI was calculated with the appendicular skeletal muscle mass in kilograms divided by the square of height in metres, according to Baumgartner et al. anthropometric equation[22,24].

Other variables studied were: demographic, clinical, analytical and treatment data. The following cytokines and adipokines were measured in all patients: high-sensitivity C reactive protein serum levels (hsCRP), TNF-α, IL-6 and IL-1-β adiponectine, resistin, leptin and insulin-like growth factor-1 (IGF-1). In the complementary material the laboratory kits used were specified, as were the normality values. The tools used for cross-sectional assessment of the RA were the disease activity score of 28 joints DAS28-CRP (*Disease Activity Score 28*-C reactive protein)[25] and the health assessment questionnaire (HAQ)[26]. Physical activities was measured by the *International Physical Activity Questionnaire* (IPAQ) through Resting Metabolic Rate (MET)[27]. Adherence to the Mediterranean diet was assessed by validated questionnaire with a score >9 out of 14 considered adherent[28].

Statistical analysis

Descriptive analysis was performed of the main variables. The frequencies of qualitative variables were expressed as the number of observations and their percentage. Quantitative variables were expressed as mean ± standard deviation (SD) if distribution was normal and as mean ± interquartile range (IQR) if the opposite was true. Normality was confirmed by the Shapiro-Wilk test[29]. The main variables were compared in subjects with and without polyautoimmunity in patients with RA using the χ^2 test, the Student's t-test for normal quantiative variables and the Mann-Whitney U test for non-normal quantitative variables. Finally, a binary logistic regression model was used for identifying the factors associated with polyautoimmunity in patientswith RA as the dependent variable. The variables incorporated into the model were the significant ones in the bivariate analyses and those of clinical interest. The multicolineality of the independent variables was confirmed using the Pearson correlation coefficient. If coefficient r between two variables was > .4, we included them separately in the models and we chose the one which had the best behaviour to explain the dependent variable. A p value <.05 was considered statistically significant and the statistical programme used was R 2.4-0.

Results

Between June 2017 and September 2019, 94 patients with RA were consecutively recruited, most of them were women (78%) with a mean age (SD) of 56.5 (11.4) years.

Poliautoimmunity

As shown by Table 1, 15 of the 94 (16.0%) patients with RA had polyautoimunity and only two (2.1%) of them had MAS. Most of the patients were women (93.3%) and over half of them were obese (60%). Ninety per cent % of them presented with FR and positive antipeptide C-citrullinated antibodies (PACA) and a higher frequency of antinuclear antibodies (ANA) with anti-Ro and anti-La specificities. Almost all of them were in treatment with classical synthetic disease-modifying antirheumatic drugs (csDMARDS) (86%) and over half with disease-modifying antirheumatic drugs (DMARDS).

The AIDs most comonly asociated with RA were SS (8/94 [8,5%]) followed by autoimmune thyroiditis (4/94 [4,2%]) and psoriasis (3/94 [3,1%]) (supplementary material). Nineteen (20.2%) patients with RA had a family history of AIDs.

Anthropometric and metabolic characteristics of patients with RA and polyautoimmunity

Table 2 shows the anthropometric characteristics and body composition by DXA of patients with RA with and without polyautoimmunity. We may observe that patients with polyautoimmunity had higher BMI scores (p = .016), with there being over half of patients with grade I obesity according to WHO and Stavropoulos-Kalinoglou et al criteria.

A total of 23 (24.5%) patients with RA presented with sarcopenia, which was more prevalent in patients with polyautoimmunity than in the others (46.7% vs. 20.3%; p = .029). As may be observed in Table 3, the patients with polyautoimmunity presented with a lower percentage of total lean mass (p = .028), lean mass in arms (p = .047) and lean mass in legs (p = .051). However, the sarcopenia was not associated with the BMI, observing that the seven patients with polyautoimmunity who had sarcopenia, 1/7 were of normal weight, 3/7 overweight and 3/7 obese (p = .998).

It should also be noted that the patients with polyautoimmunity presented with higher values of total fat mass (p = .036), fat mass index (p = .019), fat mass in legs (p = .046), fat mass in trunk (p = .032) and gynoid fat mass (p = .033). BMI showed a positive correlation both with total fat mass (r = .818; p < .001) and with the fat mass index (r = .884; p < .001). However, sarcopenia was not associated with body fat content in body composition (p = .870).

Although the rate of adherence to the Mediterranean diet was similar in both groups (24.1% vs. 20.0%; p = .734), the patients with polyautoimmunity had a lower physical activity (mean [IQR]) than the patients without polyautoimmunity measured by METs (mean [IQR]: 214.5 [141,0–669,5] vs. 495.0 [230,0–792,0] months; p = .038).

Inflammatory cytokine and adipokine characteristics of patients with RA and polyautoimmunity

Leptin and resistin levels were clearly higher in patients with polyautoimmunity than in the others, but no differences were found in the adiponectin levles or in IL-6, IL-1-β, TNF-α, IGF-1 or oxidised LDL levels (Table 3).

Table 1
Characteristics of RA patients without polyautoimmunity (n = 79), patients with RA and polyautoimmunity (n = 15).

Variable	RA without polyautoimmunity (n = 79)	RA with polyautoimmunity (n = 15)	P value p
Epidemiologic			
Sex, female, n (%)	59 (74.7)	14 (93.3)	.112*
Age in years, mean (SD)	55.8 (11.8)	60.1 (8.6)	.185**
Comorbidities			
Tobacco			.748*
Non smoker, n (%)	39 (39.4)	9 (60.0)	
Tobacco history, n (%)	40 (50.6)	6 (40.0)	
Obesity, n (%)	34 (30.4)	9 (60.0)	.028*
Dyslipidaemia, n (%)	16 (20.3)	5 (33.3)	.265*
High blood pressure, n (%)	20 (25.3)	4 (26.7)	.912*
Diabetes mellitus, n (%)	4 (5.1)	0 (.0)	.373*
Clinical data			
Mean duration of disease (SD), months	98.6 (27.1)	93.0 (29.4)	.518**
Delayed diagnosis, median (IQR), months	11.3 (5.7-27.6)	6.8 (4.1-20.8)	.383[a]
Erosions, n (%)	48 (615)	11 (73.3)	.385*
Rheumatoid factor +, n (%)	64 (81.0)	14 (93.3)	.244*
ACPA +, n (%)	58 (73.4)	13 (86.7)	.274*
ANA +, n (%)	0 (.0)	8 (53.3)	<.001*
Anti-Ro +, n (%)	0 (.0)	8 (53.3)	<.001*
Anti-La +, n (%)	0 (.0)	5 (33.3)	<.001*
DAS28-ESR, mean (SD)	2.8 (1.1)	3.1 (.7)	.361**
HAQ, mean (SD)	.6 (.8)	.8 (.4)	.691**
Treatments			
Synthetic DMARDS, n (%)	67 (84.8)	13 (86.7)	.853*
Methotrexate, n (%)	56 (70.9)	10 (66.7)	.743*
Hydroxychloroquine, n (%)	5 (6.3)	0 (.0)	.317*
Leflunomide, n (%)	6 (7.6)	2 (13.3)	.465*
Sulfasalazine, n (%)	8 (7.6)	2 (13.3)	.712*
Biologic DMARD, n (%)	31 (39.2)	9 (60.0)	.099*
Anti-TNF, n (%)	23 (29.1)	7 (46.7)	.181*
Tocilizumab, n (%)	5 (6.3)	2 (13.3)	.344*
Abatacept, n (%)	1 (1.3)	0 (.0)	.661*
Rituximab, n (%)	2 (2.6)	0 (.0)	.531*

ACPA: Anti-citrullinated C-peptide Antibodies; ANA: Antinuclear Antibodies; DAS28-ESR: 28-joint Disease Activity Score; DMARDS: Disease-modifying Antirheumatic Drugs; ESR: Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; RA: Rheumatoid Arthritis; SD: Standard Deviation.

* Statistical test χ^2.

** Statistical Student's t-test.

[a] Statistical Mann-Whitney U test.

Multivariate

Table 4 shows a multivariate logistic regression analysis for the polyautoimmunity-depedent variable in patients with RA. Alhtough BMI and resistin were independetnly associated, the probabiliy of sarcopenia was almost five times greater in patients with polyautoimmunity. Also, an alternative model was made which included fat mass index instead of BMI, showing similar outcomes.

Discussion

RA is a systemic AIDs which may coexist with other well-defined AIDs in the same patient, which has been called polyautoimmunity[9]. The study of polyautoimmunity is important since the concurrence of both autoimmune diseases in the same patient may impact their prognosis[9,30,31]. Although polyautoimmunity in RA has been little researched[9], an association with obesity has recently been described which merits further, more detailed investigation[10].

In our study BMI was correlated with fat mass and fat mass indices, but not with sarcopenia. Most patients with RA and polyautoimmunity who presented with sarcopenia did not correspond to the obesity group according to their BMI, which had only already been described in non-polyautoimmune patients with RA[4].

An exhaustive comparison of body composition by DEXA revealed that 23/94 (24.5%) of our patients with RA had sarcopenia and that this was independently associated with polyautoimmunity. In keeping with this findiing, patients with RA and polyautoimmunity had a significantly lower percentage of total lean fat and lean fat in their extremities. However, total fat mass was also associated with polyautoimmunity in patients with RA. Previous studies have assessed the prevalence of sarcopenia in patients with RA between 20% and 43.3%[1,4]. These data are concordant with the percentage of sarcopenia found in our total patient sample (24.5%), although they are somewhat lower when compared with the patients with RA and polyautoimmunity (46.7%). Sarcopenia and increased fat mass in patients with RA has been associated with increased cardiovascular risk, greater morbidity and higher mortality[32–35].

Among the factors related to sarcopenia and increased fat mass in patients with RA is lack of physical activity, disability, inflammatory activity of disease and the effect of adipokines and chemokines[1]. Related to this, our patients with poliautoimmunity did less physical activity than the others, measured by Mets. Fatigue and reduced physical activity may lead to loss of strength and function, which could lead to a progressive loss of muscle mass and a higher risk of developing sarcopenia[36]. Another study associated inflammatory activity in RA measured by DAS28 with a higher percentage of sarcopenia and increased fat mass[1]. In our study, despite the fact that the patients with RA and polyautoimmunity presented with higher DAS28-ESR values, these differences were not significant. This could be due to the fact that 60% of patients with RA and polyautoimmunity received biologics compared with 39% of RA with no polyautoimmunity, and this could have had an impact

Table 2
Anthropometric and metabolic characteristics of patients with RA and polyautoimmunity.

Variable	RA without polyautoimmunity (n = 79)	RA with polyautoimmunity (n = 15)	P value
Anthropometric characteristics			
BMI (kg/m^2), mean (SD)	27.7 (4.6)	31.0 (5.8)	.016**
BMI classification (WHO)			.014*
Low weight (BMI < 18.5), n (%)	0 (.0)	0 (.0)	
Normal weight (BMI 18.5-24.9), n (%)	27 (34.2)	2 (13.3)	
Overweight (BMI 25.0-29.9), n (%)	28 (35.4)	2 (13.3)	
Grade I obesity (BMI 30.0-34.5), n (%)	20 (25.3)	9 (60.0)	
Grade II obesity (BMI 35.0-39.9), n (%)	2 (2.5)	0 (.0)	
Grade III obesity (BMI ≥ 40), n (%)	2 (2.5)	2 (13.3)	
Waist circumference (cm), mean (SD)	90.4 (11.3)	93.0 (14.1)	.343**
Hip circumference (cm), mean (SD)	103.0 (6.7)	105.0 (9.5)	.213**
Waist to hip ratio, mean (SD)	.8 (.0)	.8 (.1)	.745**
Stavropoulos-Kalinoglou et al.[20] classification			.025*
Low weight (BMI < 18), n (%)	0 (.0)	0 (.0)	
Normal weight (BMI 18.0-22.9), n (%)	12 (15.2)	1 (6.7)	
Overweight (BMI 23.0-27.9), n (%)	34 (43.0)	2 (13.3)	
Obesity (BMI ≥ 28), n (%)	33 (41.8)	12 (80.0)	
Body composition measured by DXA			
Sarcopenia, n (%)	16 (20.3)	7 (46.7)	.029*
RSMI, mean (SD)	6.8 (2.8)	6.4 (1.5)	.470**
Total fat mass (kg), mean (SD)	28.5 (9.5)	35.6 (10.1)	.036**
FMI (kg/m^2), mean (SS)	39.9 (11.8)	43.8 (13.1)	.019**
Total lean mass (kg), mean (SD)	40.8 (9.2)	38.0 (4.9)	.198**
Lean mass (%), mean (SD)	.57 (.1)	.51 (.1)	.028**
FFMI (kg/m^2), mean (SD)	52.4 (9.4)	48.9 (8.5)	.106**
Fat mass armss (kg), median (IQR)	2.6 (1.9-3.3)	3.7 (2.0-4.1)	.090[a]
Fat mass legs (kg), mean (SD)	9.7 (3.8)	11.6 (3.9)	.046**
Fat mass trunk (kg), mean (SD)	14. 9 (5.5)	17.8 (4.8)	.032**
Android fat mass (kg), mean (SD)	2.5 (1.0)	2.9 (1.2)	.119**
Gynoid fat mass (kg), mean (SD)	4.9 (1.6)	6.1 (1.4)	.033**
Lean mass arms (kg), median (IQR)	3.7 (3.2-5.1)	3.3 (3.2-4.4)	.067[a]
Lean mass legs (kg), mean (SD)	1.2 (3.0)	1.1 (1.4)	.051**
Lean mass trounk (kg), mean (SD)	2.0 (4.5)	1.9 (2.7)	.438**
Android lean mass (kg), mean (SD)	2.9 (.7)	2.8 (.4)	.816**
Gynoid lean mass (kg), mean (SD)	5.8 (1.2)	5.6 (.8)	.643**
Physical activity and Mediterranean diet			
RMRs, median (IQR)	495.0 (230.0-792.0)	214.5 (141.0-669.5)	.038[a]
Predimed (> 9), n (%)	19 (24.1)	3 (20.0)	.734*

BMI: Body Mass Index; DXA: Dual-energy X-ray Absorptiometry; FFMI: Fat-free Mass Index; FMI: Fat Mass Index; IQR: Interquartile Range; RA: Rheumatoid Arthritis; RMR: Resting Metabolic Rate; RSMI: Relative Skeletal Mass Index; SD: Standard Deviation; WHO: World Health Organisation.

* χ^2 Statistical test.

** Student's t statistical test.

[a] Mann-Whitney U statistical test.

Table 3
Inflammatory cytokine and adipokine profile of patients with RA and polyautoimmunity.

Variable	RA without polyautoimmunity (n = 79)	RA with polyautoimmunity (n = 15)	P value p[b]
Interleukines and adipokines			
Leptin, p 5-p95*,[a]	21.8 (18.0)	35.4 (22.6)	.022
Resistin, ng/mL*	7.2 (2.6)	9.6 (5.4)	.027
Adiponectin, μg/mL**	11,265.6 (7,767.6-15,045.5)	12,132.2 (7,926.1-14,802.5)	.886
IL6, pg/mL**	10.5 (5.4-19.2)	15.8 (5.1-113.4)	.526
PCR, mg/L**	3.1 (2.9-6.2)	4.3 (3.4-4.5)	.430
IL-1-β, pg/mL**	4.3 (4.1-4.4)	4.4 (4.1-4.7)	.560
TNF-α, pg/mL**	5.0 (3.7-23.6)	9.8 (3.4-92.8)	.256
IGF-1, pg/mL*	184.2 (101.6)	165.4 (102.2)	.606
Oxidase LDL, UI/mL**	2.5 (.8-5.6)	1.0 (.1-4.0)	.302

IGF-1: growth factor similar to insulin-1; IL-1-β: interleukin 1 beta; IL-6: interleukin 6; RA: rheumatoid arthritis; TNF-α: tumour necrosis factor alpha.

* Mean ± Standard Deviation (SD).

** Median (Interquartile Range [IQR]).

[a] according to the manufacturer, the normal values are between the percentiles 5 and 95 after djustment for gender and BMI.

[b] χ^2 Statistical test, Student's t statistical test and Mann-Whitney U statistical test.

on higher control of the inflammatory activity and of inflammatory cytokines.

It was also previously described that the elevation of inflammatory cytokines during the course of RA promotes migration of mesenchymal precursors from adipose tissue, stimulates adipose differentiation and consequently elevates adipokines, aggravating sarcopenia[37,38]. Here, in our study resistin was associated independently with polyautoimmunity. The increase of resistin levels was not only observed in other RA studies[1], but also in other autoimmune diseases such as SS[39,40] and SLE[41,42]. The adipokines secreted by the adipose tissue were shown to actively participate as mediators of rheumatic diseases[43]. Resistin is an adipokine involved in the provocation of inflammatory response through activation of the immune cell system and the production of inflammatory

Table 4
Logistic regression model 1 of characteristics associated with polyautoimmunity in patients with RA.

Variable	Bivariate OR (CI 95%)	Multivariate OR* (CI 95%)	P value
Age in years	1.036 (.983-1.091)		
Sex, female	4.746 (.586-18.414)		
Body mass index	1.133 (1.017-1.262)	1.186 (1.041-1.351)	.011
Sarcopenia	3.445 (1.087-7.338)	4.800 (1.497-13.952)	.013
Mets	.998 (.996-1.000)		
Leptin	1.032 (1.003-1.062)		
Resistin	1.201 (1.015-1.422)	1.249 (1.016-1.535)	.035

Nagelkerke R2 = .304; omnibus test = .001; Hosmer-Lemeshow test = .565.
CI: confidence interval; RA: rheumatoid arthritis.
* Variables included in the analysis; age, sex, body mass index, sarcopenia, leptin and resistin.

cytokines[44]. A positive correlation was described between resistin and inflammatory markers and also markers of cardiovascular damage, metabolic markers, arthritis, kidney disease and glandular inflamation in SS[40]. Thus resistin and other adipokines could act by stimulating inflammation and autoimmunity and also by altering body composition (more sarcopenia and an increase in fat mass), and this in turn would increase the inflammatory process even more and lead to a higher production of adipokines. In fact, in one study it was shown that resistin produced an alteration of myogenesis of the human skeletal muscle and altered the muscle metabolism in the developing myotubes. These findings could have major implications for maintaining muscle mass in older people with chronic inflammatory diseases or obese or overweight elderly people[45].

Our study has several limitations. Firstly, it was a cross-sectional study and we were therefore unable to establish a causal relationship. However, it did allow us to become aware of factors associated with polyautoimmunity in RA which had not been previously studied. Furthermore, it may be that the small number of men from our study made it impossible to observe the association between polyautoimmunity in RA and the female sex, although in other studies polyautoimmunity was associated with the female sex. Despite this, we were able to observe that the number of women with RA and polyautoimmunity was very high. The observation in the univariate analysis that patients with RA and polyautoimmunity had a significantly lower percentage of total lean mass and lean mass in extremities plus total fat mass and BMI, was limited by not being adjusted by other variables. Also, the limitation of multivariate analysis is the low number of patients with RA which present with polyautoimmunity. However, despite the fact that polyautoimmunity is a rare phenomenon in RA, we were able to observe in the multivariate analysis the association of polyautoimmunity in RA with BMI, sarcopenia and resistin levels.

To conclude, RA patients with polyautoimmunity had a higher prevalence of sarcopenia and obesity (according to BMI), and had higher levels of fat mass and resistin compared with RA patients without polyautoimmunity. Therefore, polyautoimmunity in patients with RA could be associated with metabolic disorders which could have a negative effect on the perpetuation of inflammatory and autoimmune processes, and be associated with higher morbimortlaity in these patients.

Financing

This study did not receive any type of financing.

Conflict of interests

The authors have no conflict of interests to declare.

Acknowledgements

Our thanks to the microbiology services, to Dr. Yolanda Aguilar Lizarralde, and to the emergency and infectious disease units of the participating hospital centres.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reumae.2021.06.002.

References

1. Brance ML, Di Gregorio S, Pons-Estel BA, Quagliato NJ, Jorfen M, Berbotto G, et al. Prevalence of Sarcopenia and Whole-Body Composition in Rheumatoid Arthritis. J Clin Rheumatol. 2020, http://dx.doi.org/10.1097/RHU.0000000000001549.
2. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.
3. Greenlund LJ, Nair KS. Sarcopenia-consequences, mechanisms, and potential therapies. Mech Ageing Dev. 2003;124:287–99.
4. Ngeuleu A, Allali F, Medrare L, Madhi A, Rkain H, Hajjaj-Hassouni N. Sarcopenia in rheumatoid arthritis: prevalence, influence of disease activity and associated factors. Rheumatol Int. 2017;37:1015–20.
5. Doğan SC, Hizmetli S, Hayta E, Kaptanoğlu E, Erselcan T, Güler E. Sarcopenia in women with rheumatoid arthritis. Eur J Rheumatol. 2015;2:57–61.
6. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging. 2008;12:433–50.
7. Giles JT, Ling SM, Ferrucci L, Bartlett SJ, Andersen RE, Towns M, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. Arthritis Rheum. 2008;59:807–15.
8. Rojas-Villarraga A, Toro CE, Espinosa G, Rodríguez-Velosa Y, Duarte-Rey C, Mantilla RD, et al. Factors influencing polyautoimmunity in systemic lupus erythematosus. Autoimmun Rev. 2010;9:229–32.
9. Rojas-Villarraga A, Amaya-Amaya J, Rodriguez-Rodriguez A, Mantilla RD, Anaya JM. Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. Autoimmune Dis. 2012;2012:254319.
10. Ordoñez-Cañizares MC, Mena-Vázquez N, Redondo-Rodriguez R, Manrique-Arija S, Jimenez-Núñez FG, Ureña-Garnica I, et al. Frequency of Polyautoimmunity in Patients With Rheumatoid Arthritis and Systemic Lupus Erythematosus. J Clin Rheumatol. 2020, http://dx.doi.org/10.1097/RHU.0000000000001574.
11. Mena-Vázquez N, Fernández-Nebro A, Pego-Reigosa JM, Galindo M, Melissa-Anzola A, Uriarte-Isacelay E, et al. Hydroxychloroquine is associated with a lower risk of polyautoimmunity: data from the RELESSER Registry. Rheumatology (Oxford). 2019;59:2043–51.
12. Barragán-Martínez C, Amaya-Amaya J, Pineda-Tamayo R, Mantilla RD, Castellanos-de la Hoz J, Bernal-Macías S, et al. Gender differences in Latin-American patients with rheumatoid arthritis. Gend Med. 2012;9:490–510.e5.
13. Gremese E, Tolusso B, Gigante MR, Ferraccioli G. Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Front Immunol. 2014;5:576.
14. Winer S, Paltser G, Chan Y, Tsui H, Engleman E, Winer D, et al. Obesity predisposes to Th17 bias. Eur J Immunol. 2009;39:2629–35.
15. Arai S, Miyazaki T. Impacts of the apoptosis inhibitor of macrophage (AIM) on obesity-associated inflammatory diseases. Semin Immunopathol. 2014;36:3–12.
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81.

17. Anaya JM, Castiblanco J, Rojas-Villarraga A, Pineda-Tamayo R, Levy RA, Gomez-Puerta J, et al. The multiple autoimmune syndromes. A clue for the autoimmune tautology. Clin Rev Allergy Immunol. 2012;43:256–64.
18. Anaya JM, Corena R, Castiblanco J, Rojas-Villarraga A, Shoenfeld Y. The kaleidoscope of autoimmunity: multiple autoimmune syndromes and familial autoimmunity. Expert Rev Clin Immunol. 2007;3:623–35.
19. WHO. Obesity Preventing and managing the global epidemic. Geneva: WHO; 1997.
20. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Kitas GD. Obesity in rheumatoid arthritis. Rheumatology (Oxford). 2011;50:450–62.
21. WHO. Physical status: the use and interpretation of anthropometry, report of a WHO expert committee. Geneva: WHO; 1995.
22. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147:755–63.
23. Delmonico MJ, Harris TB, Lee JS, Visser M, Nevitt M, Kritchevsky SB, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. J Am Geriatr Soc. 2007;55:769–74.
24. Walsh MC, Hunter GR, Livingstone MB. Sarcopenia in premenopausal and postmenopausal women with osteopenia, osteoporosis and normal bone mineral density. Osteoporos Int. 2006;17:61–7.
25. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44–8.
26. Esteve-Vives J, Batlle-Gualda E, Reig A. Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. Grupo para la Adaptación del HAQ a la Población Española. J Rheumatol. 1993;20:2116–22.
27. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International Physical Activity Questionnaire: 12-country Reliability and Validity. Med Sci Sports Exerc. 2003;35:1381–95.
28. Appel LJ, Van Horn L. Did the PREDIMED trial test a Mediterranean diet? N Engl J Med. 2013;368:1353–4.
29. Filion GJ. The signed Kolmogorov-Smirnov test: why it should not be used. Gigascience. 2015;4:9.
30. Valerio G, Maiuri L, Troncone R, Buono P, Lombardi F, Palmieri R, et al. Severe clinical onset of diabetes and increased prevalence of other autoimmune diseases in children with coeliac disease diagnosed before diabetes mellitus. Diabetologia. 2002;45:1719–22.
31. Avouac J, Airò P, Dieude P, Caramaschi P, Tiev K, Diot E, et al. Associated autoimmune diseases in systemic sclerosis define a subset of patients with milder disease: results from 2 large cohorts of European Caucasian patients. J Rheumatol. 2010;37:608–14.
32. Bianchi G, Rossi V, Muscari A, Magalotti D, Zoli M. Physical activity is negatively associated with the metabolic syndrome in the elderly. QJM. 2008;101:713–21.
33. Mena-Vázquez N, Rojas-Gimenez M, Jimenez Nuñez FG, Manrique-Arija S, Rioja J, Ruiz-Limón P, et al. Postprandial Apolipoprotein B48 is Associated with Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis. J Clin Med. 2020;9.
34. Delgado-Frías E, González-Gay MA, Muñiz-Montes JR, Gómez Rodríguez-Bethencourt MA, González-Díaz A, Díaz-González F, et al. Relationship of abdominal adiposity and body composition with endothelial dysfunction in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2015;33:516–23.
35. Delgado-Frías E, López-Mejias R, Genre F, Ubilla B, Gómez Rodríguez-Bethencourt MA, González-Díaz A, et al. Relationship between endothelial dysfunction and osteoprotegerin, vitamin D, and bone mineral density in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2015;33:241–9.
36. Montero-Fernández N, Serra-Rexach JA. Role of exercise on sarcopenia in the elderly. Eur J Phys Rehabil Med. 2013;49:131–43.
37. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev. 2017;35:200–21.
38. Gálvez BG, San Martín N, Rodríguez C. TNF-alpha is required for the attraction of mesenchymal precursors to white adipose tissue in Ob/ob mice. PLoS One. 2009;4:e4444.
39. Augusto KL, Bonfa E, Pereira RM, Bueno C, Leon EP, Viana VS, et al. Metabolic syndrome in Sjögren's syndrome patients: a relevant concern for clinical monitoring. Clin Rheumatol. 2016;35:639–47.
40. Boström EA, d'Elia HF, Dahlgren U, Simark-Mattsson C, Hasséus B, Carlsten H, et al. Salivary resistin reflects local inflammation in Sjögren's syndrome. J Rheumatol. 2008;35:2005–11.
41. Chougule D, Nadkar M, Venkataraman K, Rajadhyaksha A, Hase N, Jamale T, et al. Adipokine interactions promote the pathogenesis of systemic lupus erythematosus. Cytokine. 2018;111:20–7.
42. Baker JF, Morales M, Qatanani M, Cucchiara A, Nackos E, Lazar MA, et al. Resistin levels in lupus and associations with disease-specific measures, insulin resistance, and coronary calcification. J Rheumatol. 2011;38:2369–75.
43. Gómez R, Conde J, Scotece M, Gómez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? Nat Rev Rheumatol. 2011;7:528–36.
44. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59:1690–7.
45. O'Leary MF, Wallace GR, Davis ET, Murphy DP, Nicholson T, Bennett AJ, et al. Obese subcutaneous adipose tissue impairs human myogenesis, particularly in old skeletal muscle, via resistin-mediated activation of NFκB. Sci Rep. 2018;8:15360.