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Dual X-ray absorptiometry whole body composition of adipose tissue in rheumatoid arthritis

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Aim. Rheumatoid arthritis (RA) may influence not only abdominal fat, but also whole body adiposity, since it is associated with chronic inflammation and disability. The study aims to evaluate the whole body adiposity of RA patients and to assess potential influences of disease specific measures.

Methods. The study was designed to include Caucasian postmenopausal female RA patients and age-matched postmenopausal female controls. Each subject underwent on the same day clinical examination, laboratory tests, whole body dual X-ray absorptiometry (DXA) composition and physical activity estimation using a self-administered questionnaire.

Results. A total of 107 RA women and 104 matched controls were included. Compared to controls, the RA group had less physical activity and a higher prevalence of normal weight obesity. Overfat RA women had a significantly higher toll of inflammation, disease activity, glucocorticoid treatment and sedentary behavior. RA women with inflammation, glucocorticoid treatment and higher disease activity class had higher whole body and trunk adipose tissue indices and higher prevalence of overfat status. Glucocorticoid treatment, inflammation, disease duration and severity correlated with whole body adipose tissue and significantly predicted high adiposity content and overfat phenotypes.

Conclusions. RA disease duration and severity are associated with higher whole body and regional adiposity. Low-dose glucocorticoid treatment seems to contribute to adiposity gain and redistribution. Clinicians may need to assess body composition and physical activity in RA patients in order to fully manage cardiovascular outcomes and quality of life.

Key words: rheumatoid arthritis, DXA body composition, adipose tissue, obesity.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a progressive auto-immune disease characterized by chronic inflammation which leads to joint deformity, disability, distress and socio-economic costs. RA is also associated with modifications of the body composition. The mass and distribution of fat, muscle and bone are equally changed by RA [1], even in the early stages [2-4]. The RA-adipose tissue interaction entails central adiposity, the metabolic syndrome (MetS) and obesity classically defined by a body mass index (BMI) above 30 kg/m^2. It seems that BMI-defined obesity has a comparable prevalence among RA and general populations [5], a figure which may be underestimated by the fact that the classical BMI cutoffs are too high for RA patients (for a given body fat content, RA patients had a BMI with 2 kg/m^2 lower than controls, probably due to the loss of muscle mass and to the gain of fat mass) [6]. Another drawback of BMI is the lack of information regarding the actual amount and distribution of fat, knowing that central obesity and the MetS are highly prevalent in RA patients [7-9]. The study of these conditions is relevant clinically, since adipose tissue disturbances increase the cardiovascular risk [10], but also for fundamental research, since there are reports of bidirectional pathological relationships [11]. The assessment of body composition in RA was mostly done using anthropometry and bioimpedance [12, 13], while the use of dual X-ray absorptiometry (DXA) technique was limited [3, 4, 14, 15]. Most of the studies included both genders, despite the facts that RA is more prevalent among women and that body composition differs significantly between genders. In this context,we hypothesized that there must be a specific effect of RA measures on whole body adiposity, not exclusively on abdominal fat, since the disease is associated with a number of factors which can influence the adipose tissue (e.g. inflammation, disability, glucocorticoids). Therefore, the study aims to evaluate the whole body adiposity RA patients using DXA and to assess potential influences of disease measures on body composition phenotypes.

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2. METHODS

2.1. PATIENTS AND CRITERIA

The study was designed to include all the female patients admitted to our Rheumatology Department (Research Centre of the Pathology and Treatment of Systemic Rheumatic Diseases – RCRD, Bucharest) in the random order of presentation between May and August 2014. The inclusion criteria were: female sex (since RA is more frequent in women and since men have largely different body composition phenotypes than women), Caucasian race, postmenopausal status, 2010 ACR/EULAR classification criteria for RA [16], a RA disease duration longer than 6 months. Age-matched healthy Caucasian post-menopausal female subjects were randomly selected and invited to participate in the study using the records of general practitioners associated with RCRD from the same geographic area. The following exclusion criteria were applied for both groups: weight > 150 kg (DXA table weight limit); current cancer; digestive pathology (gastrectomy, bariatric or intestinal surgery, primary biliary cirrhosis, celiac disease, malabsorption); chronic obstructive lung disease; severe heart failure (New York Heart Association classify-cation ≥ 3); moderate-severe chronic kidney disease (glomerular filtration rate < 60 mL/min/1.73 m^2); endocrine abnormalities (hyperthyroidism, hyperpara-thyroidism, hypogonadism); psychiatric eating disorder, therapy with any of the following drugs in the last 6 months: estrogen-replacement therapy, glucocorticoids exceeding 7.5 mg/day prednisone equivalent, antipsychotics, orlistat, lorcaserin, exo-genous insulin. Each patient gave written informed consent and the study was approved by the local ethics committee. The clinical examination, laboratory tests and DXA body composition analysis were done on the same day for each patient.

2.2. CLINICAL EXAMINATION

A clinical interview and a review of the medical history recorded age, smoking status, disease duration, duration of morning stiffness, patient global self assessment of general health and disease activity (visual analog scale), treatment regimes and extra-articular manifestations (rheumatoid nodules, vasculitis, neurologic, pulmonary, cardiac, renal or ophthalmologic involvement). Quality of life was assessed using a self-administered modified health assessment questionnaire (HAQ) [17]. A single senior author rheumatologist (DO) performed systematical clinical examinations, which focused on anthropometrics and RA variables. The classic anthropometric indices such as height, weight, waist and hip circumferences (WC, HC) were measured in upright anatomical position, light clothes, without shoes, using a mechanical scale (0.1 kg maximal error), a stadiometer (0.3 cm maximal error) and a centimeter graded stretch resistant tape. For WC, the tape was placed horizontally and directly on skin, midway between the last rib and the iliac crest, and read at the end of a normal exhalation. For HC, the tape was placed horizontally around the widest portion of the buttocks. The waist-to-hip ratio (WHR) was calculated dividing WC to HC. Body mass index (BMI) was calculated dividing weight by the square of height. Obesity and overweight were defined using the World Health Organization (WHO) cutoffs of BMI ≥ 30 kg/m^2 and 25 kg/m^2 respectively. The clinical examination accounted for the number of painful and swollen joints (bilateral proximal interphalan-geal, metacarpophalangeal, wrist, elbow, shoulder, knee joints) and identified patients with RA joint deformities of their hands (henceforth designated "joint deformity"): fixed flexion contracture, ulnar deviation, "swan neck", "boutonniere", "Z" thumb, other luxations and subluxations, impaired range of motion, arthritis mutilans. A visual analog scale indication of the global disease activity was recorded by the evaluator. A single senior author rheumatologist (VB) identified radiological damage on standard postero-anterior X-ray images of the hands and feet. The Simple Erosion Narrowing Score (SENS) was calculated using the method proposed by van der Heijde *et al.* [18].

2.3. LABORATORY MEASURES

All the included patients underwent morning venipuncture and blood samples were tested with commercial kits for routine blood chemistry and complete blood count, erythrocyte sedimentation rate (ESR; Westergren method), C-reactive protein (CRP; nephelometric method), IgM rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA; enzyme-linked immunosorbent assay). Inflammation was classified if either CRP or VSH were above the upper limit of normal (5 mg/L and 30 mm/h respectively), in the absence of other causes than RA. Using the clinical and laboratory measures, RA activity was assessed using two composite tools: disease activity score (DAS28; remission ≤ 2.6; low disease activity – LDA 2.6-3.2; moderate disease activity – MDA 3.2-5.1; high

disease activity – HDA > 5.1) [19], and clinical disease activity index (CDAI; remission ≤ 2.8; LDA 2.9-10; MDA 10.1-22; HDA ≥ 22.1) [20].

2.4. DXA WHOLE BODY COMPOSITION

Body composition was evaluated by whole body less head DXA with a Lexxos C05LX223 densitometer. All the scans were performed by a single certified clinical densitometrist (CP; 0.48% variation coefficient). Daily calibration and quality control tests were performed according to the manufacturer's recommendations and different regions of interest were manually checked for maximal reliability [21]. The patients were required to wear light clothing, without metal or plastic, and were scanned in the morning, after nocturnal fast, micturition and 5-10 minutes of supine rest on the examination table, in the absence of radioactive or radiocontrast investigations in the last week. Data records included whole body and regional (trunk, pelvis, arms, legs) variables such as adipose tissue density/mass/area/percent (wbATD/M/A/P). Appendicular adipose mass (AAM) was calculated as the sum of the adipose tissue masses of all four members, while the appendicular adipose density (AAD) was calculated as the arithmetic mean of the adipose tissue densities of all four members. Fat mass index (FMI) was calculated in two ways: dividing wbATM to weight (FMI1) or to square height (FMI2). Fat distribution ratio (FDR) was calculated either by dividing trunk adipose mass (TAM) by AAM (FDR1) or by dividing pelvic ATM by AAM (FDR2). Using the concepts of Lorenzo *et al.* [22], the patients were further categorized with normal weight obesity (NWO; BMI < 25 kg/m^2 and wbATP> 30%) and pre-obese obesity (POO; BMI > 25 kg/m^2 and wbATP> 30%). The metabolic syndrome (MetS) was defined using the 2006 International Diabetes Foundation criteria [23]. Using the DXA-derived cutoffs of wbATP proposed by Gallagher *et al.* [24] and the bioelectrical impedance analysis (BIA) cutoffs of FMI2 and wbATP proposed by Schutz *et al.* [25] and by Abernathy *et al.* [26] respectively, over 95% of our RA patients were overfat. In the absence of specific Romanian population cutoffs for whole body composition, we used our non-RA group as reference population. Accordingly, overfat status was classified either with a percent cutoff (wbATP above the 66th percentile of the reference group, corresponding to 65.71%) or with an absolute cutoff (FMI2 above the 66th percentile of the reference group, corresponding to 18.51 kg/m^2).

2.5. PHYSICAL ACTIVITY ESTIMATION

Physical activity was estimated using the self-administered Global Physical Activity Questionnaire version 2 (GPAQ2), developed by WHO, with a total of 16 questions in 4 activity sections (work, travel, recreational, sedentary) [27, 28]. The English questionnaire was translated into Romanian by the authors and back-translated by an independent authorized translator. The final version of the Romanian version was pre-tested on a random sample of 15 healthy employees and 15 RA patients from RCRD.

2.6. STATISTICS

Data distribution normality was assessed using descriptive statistics, normality, stem-and-leaf plots and the Lillefors corrected Kolmogorov-Smirnov test. Qualitative data were expressed as "absolute value (percentage of group)" and were studied using cross-tabs with χ^2 or Fisher tests. Non-normally distributed scale data were reported as "median (interquartile range)" and their correlations and differences were assessed using non-parametric tests: bivariate Spearman and partial correlations for two scale variables (in order to exclude the effect of confounders on adipose tissue indices, these partial correlations were done controlling for age, BMI, physical activity, smoking and glucocorticoid use); Mann-Whitney U and Kruskal-Wallis for differences of scale variables in groups with two (e.g. smoking) or more categories (e.g. RA disease activity). To determine which categories of multi-level nominal variables produced significant χ^2 or Mann-Whitney tests, one-way ANOVA was used with post-hoc analysis (Tukey and Bonferroni multiple comparisons). To assess the independent predictive capacity of RA-variables, logistic regression models were created using adipose tissue phenotypes (binary logistic regression) or adipose tissue scale variables (standard multivariate linear regression) as dependents and RA variables and confounding variables as covariates; the scale variables included in the models were normalized using arithmetic functions (indicated in text). All tests were considered significant if $p < 0.05$ and were done using IBM SPSS v.20 (IBM Inc., Armonk, N.Y., 2010) for Windows and GraphPad Prism 6.0 (GraphPad Software, La Jolla California, USA).

3. RESULTS

3.1. GENERAL CHARACTERISTICS

The study included 107 RA postmenopausal female patients and 104 matched controls with regard to age and postmenopausal status (Table 1). Compared to controls, the RA group had a lower median BMI, less physical activity and a higher prevalence of NWO. Even though taken independently whole body adipose tissue indices, waist and hip circumferences did not differ significantly; when the former are normed by the latter significant differences appear (for example when wbATM was divided by the square of HC).

Table 1
General characteristics and comparison of the study groups

	non-RA (n = 104)	*RA (n = 107)*	*p*
age (years)	56 (48-78)	56 (46-76)	0.718
smoking (n)	21 (20.2%)	18 (16.8%)	0.098
height (m)	1.58 (0.08)	1.60 (0.08)	0.086
weight (kg)	72 (23)	69 (7)	0.108
BMI (kg/m^2)	28.6 (7.1)	26.7 (6.3)	*0.007*
BMI normal weight (n)	17 (16.3%)	34 (31.8%)	*0.028*
BMI overweight (n)	41 (39.4%)	48 (44.8%)	0.491
BMI obesity (n)	46 (44.2%)	25 (23.3%)	*0.007*
WC (cm)	95.5 (18.5)	93.5 (14.9)	0.494
HC (cm)	106 (16.3)	106 (13)	0.739
WHR	0.89 (0.06)	0.88 (0.07)	0.259
MetS (n)	65 (62.5%)	63 (58.9%)	0.711
wbATD (g/cm^2)	7.86 (2.76)	7.61 (2.22)	0.276
wbATM (kg)	40.3 (20.2)	39.5 (15.2)	0.330
wbATA (m^2)	0.52 (0.07)	0.52 (0.06)	0.454
wbATP (%)	61.7 (13.1)	62.7 (13.9)	0.758
TAD (g/cm^2)	13.1 (9.1)	12.2 (8.1)	0.252
TAM (kg)	0.91 (0.63)	0.93 (0.55)	0.758
ATD_{pelvis} (g/cm^2)	11.8 (4.3)	11.1 (3.9)	0.207
ATM_{pelvis} (kg)	7.7 (5.1)	7.7 (3.5)	0.985
AAD (g/cm^2)	5.75 (1.41)	5.64 (1.31)	0.509
AAM (kg)	19.7 (6.1)	19.2 (6.8)	0.258
FDR1 (%)	4.53 (2.38)	4.78 (2.32)	0.170
FDR2 (%)	39.4 (13.5)	40.4 (10.2)	0.175
NWO (n)	17 (16.3%)	34 (31.8%)	*0.028*
POO (n)	41 (39.4%)	46 (42.9%)	0.599
FMI1 (%)	57.3 (11.9)	58.1 (13.2)	0.904
FMI2 (kg/m^2)	16.7 (6.9)	15.5 (5.9)	0.123
FMI2-overfat (n)	35 (33.7%)	26 (24.3%)	0.171
wbATP-overfat (n)	35 (33.7%)	37 (34.6%)	0.956
ATD_{pelvis}/WC (mg/cm^3)	12.6 (2.9)	11.9 (3.1)	*0.040*
wbATM/HC^2 (kg/m^2)	3.64 (0.77)	3.49 (0.69)	*0.045*
ATD_{pelvis}/HC (mg/cm^3)	108 (30)	105 (29)	*0.043*
AAM/HC^2 (kg/m^2)	1.73 (0.36)	1.67 (0.25)	*0.032*
TPA (kMET-min/week)	5.2 (0.7-13.7)	4.7 (0.5-11.3)	*0.041*
MTT (min/week)	14 (0-154)	11 (0-103)	*0.045*
SB (min/day)	120 (60-480)	300 (30-660)	*0.033*
levels of physical activity			
low (n)	7 (6.7%)	14 (13.1%)	
moderate (n)	34 (32.7%)	40 (37.4%)	*0.042*
high (n)	63 (60.6%)	53 (49.5%)	

Notes: variables are reported as "median (interquartile range)" and "value (percent of group)"; p values represent the significance level of the test used to assess differences: Mann-Whitney (scale test variables); χ^2 (nominal test variables).

Abbreviations: AAD/M - appendicular adipose density/mass; AT D/M/A/P - adipose tissue density/mass/area/percent; BMI - body mass index; FDR - fat distribution ratio; FMI - fat mass index; MetS - metabolic syndrome; NWO - normal weight obesity; POO - pre-obese obesity; RA - rheumatoid arthritis; TAD/M - trunk adipose density/mass; TPA – total physical activity; wb - whole body; W/HC - waist/hip circumference; WHR - waist-to-hip ratio.

3.2. RA-SPECIFIC VARIABLES

Dividing the RA group into body composition phenotypes yielded significant differences between the respective subgroups regarding RA-specific variables (Table 2). Thus, overfat RA patients had a significantly higher toll of inflammation, disease activity, glucocorticoid treatment and sedentary behavior (median of 360 min/day compared to 240 min/day; p = 0.045). RA patients with the MetS had a lower prevalence of extra-articular manifestations (15.4% compared to 33.3%; p = 0.04) and a higher rate of DMARD (95.4% compared to 80.9%; p = 0.036) and GC (55.4% compared to 33.3%; p = 0.042) treatment. RA patients with POO had a higher rate of RF-positivity (100% compared to 78.8%; p = 0.005) and lower rate of DMARD treatment (80.5% compared to 95.5%; p = 0.045).

Dividing the RA group into RA phenotypes also resulted in significantly different respective subgroups regarding RA-specific variables (Table 3). Generally, patients with inflammation, glucocorticoid treatment and higher disease activity class had higher medians of whole body adipose tissue indices and higher rates of dysmetabolic phenotypes. Patients with $DAS28_{ESR}$-MDA had a significantly higher median wbATP than patients with DAS28ESR-remission (65.7% compared to 55.2%; p = 0.039).

Table 2
RA-specific variables and their differences in overfat patients

	all	*FMI2-overfat*		*wbATP-overfat*	
	(n = 107)	no (n = 81)	yes (n = 26)	no (n = 70)	yes (n = 37)
age (y)	56 (18)	55 (19)	57 (14)	55 (18)	58 (16)
ESR (mm/h)	30 (36)	26 (33)	38 (36)§	25 (31)	42 (43)§
CRP (mg/L)	6.8 (18.8)	4.4 (14.9)	17.2 (24.1)§	3.9 (17.2)	12.5 (23.9)§
inflammation (n)	70 (65.4%)	47 (58.1%)	23 (88.5%)§	39 (55.7%)	31 (83.8%)§
RA duration (y)	10 (12)	9 (10)	13 (19)	9 (10)	13 (18)
stiffness (min)	30 (80)	30 (80)	30 (80)	30 (120)	30 (45)
joint deformity (n)	77 (71.9%)	59 (72.8%)	18 (69.2%)	51 (72.9%)	26 (70.3%)
EAM (n)	24 (22.4%)	19 (23.5%)	5 (19.2%)	18 (25.7%)	6 (16.2%)
RN (n)	21 (19.6%)	16 (19.8%)	5 (19.2%)	15 (21.4%)	6 (16.2%)
RF+ (n)	93 (86.9%)	69 (85.2%)	24 (92.3%)	60 (85.7%)	33 (89.2%)
ACPA+ (n)	94 (87.8%)	71 (87.7%)	23 (88.5%)	60 (85.7%)	34 (91.9%)
DMARD* (n)	96 (89.7%)	70 (86.4%)	26 (100%)§	62 (88.6%)	34 (91.9%)
biologics# (n)	35 (32.7%)	26 (32.1%)	9 (34.6%)	23 (32.9%)	12 (32.4%)
GC (n)	49 (45.8%)	32 (39.5%)	17 (65.4%)§	28 (40.0%)	21 (56.8%)§
$DAS28_{ESR}$	4.38 (1.81)	4.11 (2.12)	4.62 (0.87)§	4.01 (2.21)	4.64 (1.05)§
$DAS28_{CRP}$	3.94 (1.64)	3.81 (1.89)	4.11 (0.89)	3.52 (1.93)	3.99 (0.97)
CDAI	13.6 (11.5)	13.2 (11.9)	14.1 (9.3)	12.9 (12.7)	15.6 (8.2)§
HAQ	0.63 (0.75)	0.63 (0.88)	0.88 (0.55)	0.56 (0.75)	0.86 (0.56)§
SENS	22 (28)	21 (22)	39 (43)	21 (19)	36 (39)§
$DAS28_{ESR}$ disease activity§					
remission (n)	11 (10.3%)	11 (13.6%)	0 (0%)	11 (15.7%)	0 (0%)
low (n)	13 (12.1%)	13 (16.1%)	0 (0%)	12 (17.1%)	1 (2.7%)
moderate (n)	54 (50.5%)	34 (41.9%)	20 (76.9%)	28 (40.0%)	26 (70.3%)
high (n)	29 (27.1%)	23 (28.4%)	6 (23.1%)	19 (27.1%)	10 (27.1%)
CDAI disease activity					
remission (n)	6 (5.6%)	6 (7.4%)	0 (0%)	6 (8.6 %)	0 (%)
low (n)	25 (23.4%)	22 (27.2%)	3 (11.5%)	21 (30.0%)	4 (10.8%)
moderate (n)	61 (57%)	42 (51.9%)	19 (73.1%)	34 (48.6%)	27 (72.9%)
high (n)	15 (14%)	10 (12.3%)	5 (19.2%)	9 (12.9%)	6 (16.2%)

Notes:
* methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine;
# infliximab, etanercept, adalimumab, golimumab, certolizumab, rituximab, abatacept, tocilizumab;
- variables are reported as "median (interquartile range)" and "value (percent of group)";
- the test used to assess differences were Mann-Whitney (scale test variables); χ^2 (nominal test variables), with the following significance levels: § $p < 0.05$; non-significant if unmarked.

Abbreviations: ACPA – anti–citrullinated protein antibodies; CDAI – clinical disease activity index; CRP – C reactive protein; DAS – disease activity score; DMARD – disease-modifying antirheumatic drugs; EAM – extra-articular manifestations; ESR – erythrocyte sedimentation rate; FMI – fat mass index; GC – glucocorticoids; HAQ – health assessment questionnaire; n – number (observed value); RA – rheumatoid arthritis; RF – rheumatoid factor; RN – rheumatoid nodules; SENS – Simple Erosion Narrowing Score; wbATP – whole body adipose tissue percent; y – years.

Table 3
Significant differences among RA subgroups

	inflammation		*glucocorticoids*		*CDAI activity*		*joint deformity*	
	no (n = 37)	yes (n = 70)	no (n = 58)	yes (n = 49)	R (n = 6)	MDA (n = 61)	no (n = 30)	yes (n = 77)
wbATD (g/cm^2)	6.89 (1.87)	7.86 (2.86)*	7.28 (2.44)	8.11 (3.18)*	4.7 (3.6)	7.9 (3.2)	8.32 (3.37)	7.58 (1.98)
wbATM (kg)	34.7 (11.9)	40.7 (19.5)*	37.9 (16.9)	43.5 (19.8)*	18.8 (25.7)	40.8 (17.8)*	46.3 (19.4)	39.2 (14.8)*
wbATA (m^2)	0.52 (0.05)	0.53 (0.07)	0.52 (0.07)	0.53 (0.05)	0.44 (0.16)	0.53 (0.05)	0.55 (0.05)	0.51 (0.06)*
wbATP (%)	57.8 (10.2)	65.2 (14.5)*	59.5 (11.7)	63.3 (12.9)*	48.1 (19.8)	65.1 (12.6)*	62.5 (13.6)	63.4 (14.3)
AAD (g/cm^2)	5.28 (1.16)	5.96 (1.48)*	5.59 (1.26)	5.69 (1.82)	3.75 (2.22)	6.01 (1.37)	6.11 (1.78)	5.43 (1.24)
AAM (kg)	16.8 (5.9)	19.7 (7.3)*	18.6 (7.1)	19.3 (6.9)	11.2 (10.3)	20.2 (6.9)*	21.7 (7.6)	18.4 (5.9)*
ATD_{pelvis} (g/cm^2)	10.06 (3.71)	11.67 (3.87)*	10.7 (4.2)	11.5 (4.2)*	6.71 (4.75)	11.77 (3.45)	12.4 (4.6)	10.8 (3.5)*
ATM_{pelvis} (kg)	6.68 (2.86)	8.27 (3.87)*	7.1 (3.5)	8.3 (4.7)*	3.2 (4.8)	8.1 (3.8)*	8.9 (5.4)	7.4 (3.1)*
FMI1 (%)	53.7 (10.5)	59.6 (14.3)*	55.2 (12.3)	59.1 (13.5)*	43.3 (22.4)	58.8 (12.9)	57.7 (13.7)	58.4 (14.2)
FMI2 (kg/m^2)	14.08 (4.63)	16.34 (7.29)*	15.4 (5.5)	15.5 (8.2)	8.2 (8.4)	16.3 (6.3)*	17.2 (6.9)	15.3 (5.4)*
FDR2 (%)	40.2 (10.6)	41.1 (11.8)	37.4 (11.2)	42.7 (10.8)*	31.8 (11.9)	41.9 (9.9)	40.1 (12.1)	40.9 (10.3)
FMI2-overfat (n)	3 (8.1%)	23 (32.9%)*	9 (15.5%)	17 (34.7%)*	0 (0%)	18 (29.5%)	9 (30.0%)	17 (22.1%)
wbATP-overfat (n)	6 (16.2%)	31 (44.3%)*	16 (27.6%)	22 (44.9%)*	0 (0%)	27 (44.3%)*	12 (40.0%)	26 (33.8%)
POO (n)	17 (45.9%)	30 (42.9%)	28 (48.3%)	18 (36.7%)	1 (16.7%)	24 (39.3%)	12 (40.0%)	34 (44.2%)
MetS (n)	24 (64.8%)	40 (57.1%)	28 (48.3%)	34 (69.4%)*	1 (16.7%)	37 (60.7%)*	14 (46.7%)	50 (64.9%)*

Note: variables are reported as "median (interquartile range)" and their differences are assessed with Mann-Whitney and Kruskal-Wallis tests which are significant ($p < 0.05$) if marked with *

Abbreviations: AAD/M – appendicular adipose density/mass; ATD/M/A/P - adipose tissue density/mass/area/percent; CDAI – clinical disease activity index; FDR – fat distribution ratio; FMI – fat mass index; MetS – metabolic syndrome; n – number; POO – pre-obese obesity; RA – rheumatoid arthritis; wb – whole body.

When assessing these differences, replacing absolute values of DXA adipose tissue with those obtained by dividing them either with WC or HC resulted in an increase of statistical significance of the above differences and the appearance of others with the same pattern (data not shown).

3.3. PREDICTION OF WHOLE BODY ADIPOSE TISSUE

Glucocorticoid treatment and RA variables such as inflammation, disease duration and severity (HAQ, SENS, activity indices) correlated with whole body adipose tissue in RA patients and proved to be significant predictors and risk factors for high adiposity content and overfat phenotypes (Table 4, Figure 1). RA patients with joint deformity behaved differently. On one hand they had significantly lower whole body adiposity and on the other hand, joint deformity classification was negatively correlated with fat content (significant) and overfat phenotype (non-significant).

4. DISCUSSION

4.1. RA *VERSUS* CONTROLS

Our data reveal several particularities of whole body adiposity of RA women. Even though controls had a higher median BMI and a higher rate of BMI-defined obesity, anthropometrical measurements of trunk adiposity (WC, HC, WHR) and DXA measures of whole body, appendicular and trunk adiposity did not differ significantly, indicating the tendency of central redistribution of adiposity in RA. In other words, even though they weighed less, RA women had the same amount of body fat compared to controls. Similarly, RA women had a significantly higher rate of BMI-defined normal weight but at the same time they also had a significantly higher rate of NWO, illustrating an altered body composition for the same BMI category. Most DXA studies have found higher whole body

and regional adipose tissue indices in RA women compared to controls [1, 3, 4], although others reported no such significant differences [29, 30]. This discrepancy is probably explained by the fact that most of these studies, including our own, are done on relatively small samples from culturally different populations, which may cause a significant variation of body composition in controls.

Table 4
Significant RA predictors of lean tissue scale indices

	dependent	*independent*	*r*	R^2	*B*	*SE*	*B 95% CI*
linear regression	AAD	ln(ESR)	0.27	0.06	0.37	0.18	0.02 - 0.72
	AAM	ln(ESR)	0.26	0.06	1.53	0.72	0.01 - 2.97
	wbATP	ln(ESR)	0.23	0.05	2.52	1.38	0.23 - 5.27
	wbATD	ln($\sqrt{CRP}$)	0.23	0.05	0.56	0.29	0.02 - 1.15
	wbATM	ln($\sqrt{CRP}$)	0.24	0.06	3.56	1.66	0.25 - 6.87
	wbATP	ln($\sqrt{CRP}$)	0.25	0.05	0.03	0.01	0.01 - 0.09
	ATM_{pelvis}	ln($\sqrt{CRP}$)	0.25	0.05	0.95	0.51	0.07 - 1.96
	AAD	ln($\sqrt{CRP}$)	0.24	0.06	0.38	0.19	0.01 - 0.75
	AAM	ln($\sqrt{CRP}$)	0.28	0.07	1.73	0.76	0.22 - 3.24
	FMI2	ln($\sqrt{CRP}$)	0.24	0.07	1.42	0.63	0.17 - 2.67
	wbATP	RA duration	0.26	0.07	0.24	0.11	0.03 - 0.44
	wbATP	sin(HAQ)	0.26	0.07	7.81	3.26	1.31 - 9.29
	wbATP	SENS	0.29	0.08	0.14	0.05	0.04 - 0.25
	FMI1	SENS	0.29	0.08	0.13	0.05	0.03 - 0.23
	wbATD	$DAS28_{ESR}$ class	-	0.06	1.17	0.52	0.13 - 2.21
	wbATM	$DAS28_{ESR}$ class	-	0.06	7.68	3.56	0.61 - 1.47
	AAD	$DAS28_{ESR}$ class	-	0.06	0.68	0.33	0.02 - 1.34
	AAM	joint deformity	-	0.06	–2.82	1.26	–5.3 - –0.3
	AAM	$DAS28_{ESR}$ class	-	0.07	3.16	1.35	0.47 - 5.85
	AAM	CDAI class	-	0.05	2.54	1.25	0.05 - 5.03
	ATD_{pelvis}	$DAS28_{ESR}$ class	-	0.06	1.74	0.83	0.09 - 3.39
	ATM_{pelvis}	glucocorticoids	-	0.06	1.61	0.75	0.11 - 3.11
	ATM_{pelvis}	$DAS28_{ESR}$ class	-	0.05	1.83	0.91	0.03 - 3.63
	dependent	*independent*	*OR*	R^2	*B*	*SE*	*OR 95% CI*
binary logistic regression	FMI2-overfat	CRP	1.87	0.08	0.95	0.48	1.19 - 3.21
	FMI2-overfat	inflammation	5.65	0.12	1.73	0.79	1.39 - 6.88
	FMI2-overfat	glucocorticoids	3.04	0.08	1.11	0.57	1.61 - 9.26
	wbATP-overfat	ESR	1.42	0.09	0.45	0.30	1.11 - 3.07
	wbATP-overfat	$DAS28_{ESR}$	1.55	0.08	0.44	0.22	1.31 - 2.39
	wbATP-overfat	HAQ	3.98	0.07	0.89	0.56	1.51 - 6.05
	wbATP-overfat	SENS	1.04	0.17	0.03	0.01	1.00 - 1.06
	wbATP-overfat	inflammation	4.32	0.12	1.46	0.61	1.29 - 7.39
	wbATP-overfat	$DAS28_{ESR}$ class	4.77	0.17	2.47	1.06	1.46 - 6.62

Notes: the *r* column reports two-tailed partial correlations; the other columns report standard multivariate linear regression models (for scale dependents) and binary logistic regression models (for nominal dependents); both correlations and regression models are significant ($p < 0.05$) and are adjusted for age, BMI, physical activity, glucocorticoids and smoking status (confounders added in the models); nominal variables are coded "0" for "no" or "remission and LDA" and "1" for "yes" or "MDA and HDA" respectively.

Abbreviations: AAD/M - appendicular adipose density/mass; wbATD/M/P - whole body adipose tissue density/mass/percent; BMI - body mass index; CDAI - clinical disease activity index; CI - confidence interval; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; FMI - fat mass index; HAQ - health assessment questionnaire; L/M/HAD - low/moderate/high disease activity; OR - odds ratio; RA - rheumatoid arthritis; SE - standard error; SENS - Simple Erosion Narrowing Score.

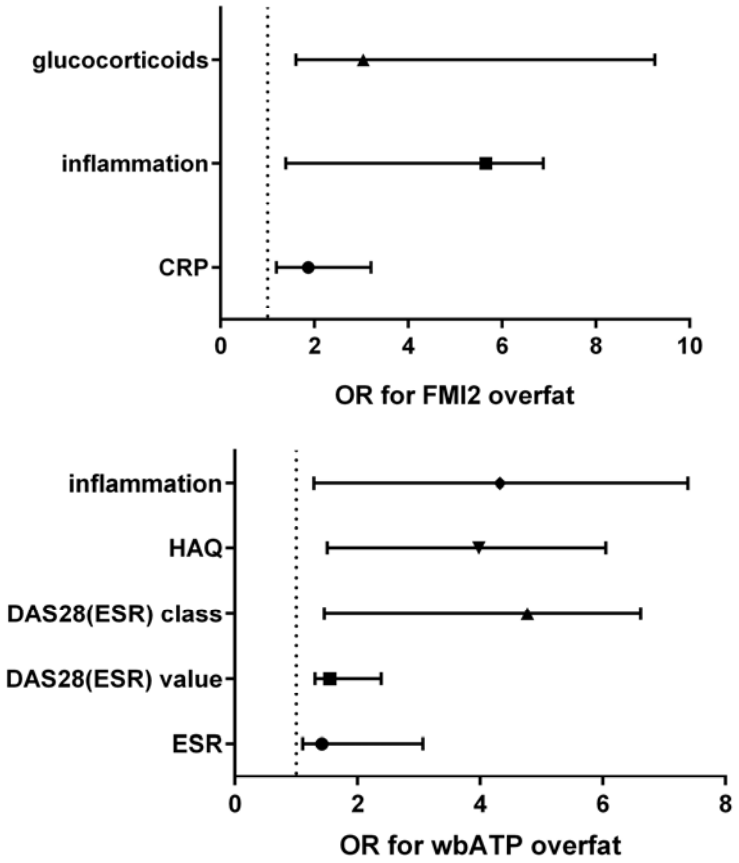

Figure 1. Significant risk factors for overfat status in RA patients (defined by two different DXA measures). Abbreviations: CRP - C-reactive protein; DAS – disease activity score; ESR - erythrocyte sedimentation rate; FMI - fat mass index; HAQ – health assessment questionnaire; OR – odds ratio; RA – rheumatoid arthritis; wbATP – whole body adipose tissue percent.

4.2. RA VARIABLES

Inflammation seems to be an important driving factor of whole body fat in RA. Compared to RA women with normal ESR and CRP, RA women with inflammation had a higher prevalence of overfat status and higher amounts of whole body and regional adiposity. Additionally, inflammation itself and inflammation markers were significant predictors and risk factors for overfat status and high whole body and regional fat content [7, 14, 31]. Conversely, overfat RA women had a higher prevalence of inflammation [1]. These quantitative and qualitative observations of a bidirectional link between inflammation and adipose tissue are in accordance with the modern pathogenic concepts of obesity as an inflammatory disorder [32, 33]. Since inflammation is inherently linked to disease activity, one would expect a significant influence of disease activity on the fat content. Indeed, in the same bidirectional manner, our overfat RA women had higher values and classes of disease activity indices, while a higher activity score or class was associated and predicted a higher adipose tissue value or state (overfat) [3, 4, 31]. The influence of inflammation and disease activity on whole body adiposity would be better assessed if one would be able to record the time duration of high inflammatory markers and high disease activity. Long-standing inflammation and high disease activity typically leads to RA joint deformity. The severity of this evolution seems to be accompanied by changes in adipose body composition. In our study, overfat RA patients had a longer disease duration and a more severe disease (HAQ, SENS, joint deformity), which were also significant predictors of adipose tissue indices and states (overfat). The significance level of these variables for predicting adiposity varies in the literature [3, 4, 7, 14], but all the studies show a positive statistical relationship with whole body and trunk adiposity. Uniquely, our RA patients with joint deformity behaved differently: they had lower whole body and regional adipose tissue indices than RA patients without joint deformity, a pattern which was also apparent from the prediction study (although statistically significant only for appendicular fat). Upon inspecting this subgroup, we found that these patients were

significantly older; they had a longer disease duration and lower body mass and BMI. Either these patients have geriatric cachexia or that is the natural course of RA-induced body composition alteration, since joint deformity is a marker of longstanding or uncontrolled disease and since it can lead to sedentary behavior, chronic pain, disability, nutrition disturbances and depression.

Treatment regimes are also associated with modification of adipose tissue quantity and distribution in RA, either directly (glucocorticoids) or indirectly by suppressing inflammation and disease activity. The reports on glucocorticoids are contradicting: some authors find as expected a positive link with whole body and/or trunk adiposity [4, 14], while others report a non-significant influence [3, 7, 29, 30]. In our sample glucocorticoid treatment made significant influences: overfat RA women had a higher frequency of glucocorticoid treatment which in turn predicted overfat status, while patients on glucocorticoids had higher whole body and regional adiposity. Since low doses of glucocorticoids can determine osteoporosis and other side effects, the gain and redistribution of fat seems a highly likely event in glucocorticoid-treated RA women. There are reports of beneficial effect of DMARD treatment on adiposity [4] and a detrimental effect of auto-immunity seropositivity [3, 4], findings which were not confirmed by our data.

4.3. STUDY LIMITATIONS

The design of the study did not allow follow-up of patients and dynamic observations of whole body adipose tissue. Data regarding diet and insulin resistance were not included in the study design. For a more thorough comparison between RA patients and controls regarding adipose tissue indices, a BMI-match may have increased the objectivity of the observation. Since the number of comparisons between variables was very high, there is an increased risk of a type I error (alpha).

5. CONCLUSION

Women with RA have a higher prevalence of normal weight obesity and exercise less compared to controls. Overfat status in RA women is associated with a significantly higher toll of inflammation, disease activity, glucocorticoid treatment and sedentary behavior. Glucocorticoids, disease activity and severity are associated and predict overfat status and whole body and regional adipose tissue indices. RA women with joint deformity and longstanding disease tend to have lower body mass and whole body adiposity. Clinicians may need to assess body composition and physical activity in RA patients in order to fully manage cardiovascular outcomes and quality of life.

Conflict of interest. No conflicts of interest relevant to this article are declared.

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Obiective. *Poliartrita reumatoidă (PR) ar putea influența nu numai adipozitatea abdominală, ci şi pe cea totală, întrucât ea se asociază cu inflamație cronică şi dizabilitate. Studiul îşi propune să evalueze țesutul adipos corporal total PR şi să cuantifice influența variabilelor specifice bolii asupra adipozității totale.*

Metode. *Studiul a inclus femei cu PR în postmenopauză şi subiecți normali de sex feminin şi vârste similare. Fiecare participant a efectuat într-o singură zi examinare clinică, teste de laborator, estimarea compoziției de masă corporală cu absorbțiometria dual cu raze X (DXA) şi evaluarea activității fizice folosind un chestionar auto-administrat.*

Rezultate. *În total, studiul a inclus 107 de paciente cu PR şi 104 subiecți normali. În comparație cu subiecții normali, pacientele cu PR prezentau nivele mai scăzute de activitate fizică şi o prevalență semnificativ mai mare a obezității normoponderale. Pacientele cu exces de țesut adipos („overfat") prezentau un nivel mai ridicat al inflamației, activității bolii, frecvenței terapiei cu glucocorticoizi şi frecvenței comportamentului sedentar. Pacientele cu inflamație, cele tratate cu glucocorticoizi şi cele cu activitate înaltă a bolii prezentau indici ai țesutului adipos total şi abdominal semnificativ mai mari, precum şi o prevalență*

mai ridicată a statutului de „overfat”. Glucocorticoizii, inflamația, durata şi severitatea bolii s-au corelat cu adipozitatea totală şi au fost factori predictivi semnificativi ai conținutului de țesut adipos şi al fenotipului „overfat”.

***Concluzii**. Durata şi severitatea PR se asociază cu adipozitate totală şi regională semnificativ mai mare. Tratamentul cu glucocorticoizi, chiar şi în doză mică, contribuie la adiția şi redistribuirea adipozității. Practicienii ar putea evalua compoziția de masă folosind DXA la pacientele cu PR în scopul unui management cardiovascular complet al acestor paciente.*

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