Relationship of abdominal adiposity and body composition with endothelial dysfunction in patients with rheumatoid arthritis

E. Delgado-Frías[1], M.A. González-Gay[2,3], J.R. Muñiz-Montes[4], M.A. Gómez Rodríguez-Bethencourt[5], A. González-Díaz[5], F. Díaz-González[1,6], I. Ferraz-Amaro[1]

[1]Division of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain;
[2]Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain;
[3]University of the Witwatersrand, Johannesburg, South Africa;
[4]IMETISA, Hospital Universitario de Canarias, Tenerife, Spain;
[5]Division of Nuclear Medicine, Hospital Universitario de Canarias, Tenerife, Spain;
[6]Department of Medicine, School of Medicine, Universidad de La Laguna, Tenerife, Spain.

Abstract

Objective

We aimed to investigate whether the abnormalities in body composition and abdominal fat that occur in rheumatoid arthritis (RA) are associated with the presence of endothelial dysfunction.

Methods

Cross-sectional study that encompassed 197 women (100 RA patients and 97 age-matched controls). Patients and controls were evaluated to establish endothelial function by brachial artery flow-mediated dilatation (FMD). Dual-x-ray-absorptiometry-derived body composition and abdominal adiposity by magnetic resonance imaging were assessed. Multiple regression analysis was performed to study the relationship between body composition and endothelial function.

Results

FMD was higher in controls compared to RA patients (8.5 [4.5–15.6] % vs. 5.3 [0.0–9.2] %, p=0.00). Appendicular-to-total lean mass ratio (0.42±0.02 vs. 0.40±0.03, p=0.00) and appendicular-to-trunk lean mass (0.82±0.08 vs. 0.78±0.08, p=0.00) were lower in RA patients. Visceral and subcutaneous abdominal fat tissues did not differ between patients and controls. Body mass index over 30 kg/m^2 was common in patients and controls (44 and 32%). High sarcopenia tended to be more elevated in RA after multivariate adjustment (13% vs. 7%, p=0.06). Fat mass index showed a negative association (per standard deviation-SD-), after adjusting for comorbidity, with FMD in controls (beta coef. -0.45[-1.05–0.05], p=0.03) but not in patients. Overfat definition (beta coef. -0.81[-1.73–0.00], p=0.05) and visceral fat (per SD beta coef. -0.60 [-1.18–0.02], p=0.04) were associated with a lower FMD values in controls but not in RA patients. Trend analysis revealed that sarcopenia was related to increased endothelial dysfunction in both patients and controls.

Conclusion

Our findings suggest that fat accumulation is not associated with endothelial dysfunction in RA patients. However, RA patients with sarcopenia are more likely to suffer endothelial dysfunction possibly being at higher cardiovascular risk.

Key words

rheumatoid arthritis, body composition, adiposity, abdominal fat tissue, endothelial function, cardiovascular disease.

Esmeralda Delgado-Frías, MD
Miguel A. González-Gay, MD, PhD
José R. Muñiz-Montes, PhD
María A. Gómez Rodríguez-Bethencourt, PhD
Antonieta González-Díaz, PhD
Federico Díaz-González, PhD
Iván Ferraz-Amaro, PhD

Please address correspondence to:
Iván Ferraz-Amaro,
Division of Rheumatology,
Hospital Universitario de Canarias,
38320 Santa Cruz de Tenerife, Spain.
E-mail: iferrazamaro@hotmail.com

Received on December 5, 2014; accepted in revised form on March 13, 2015.

Funding: this work was supported by a grant from the Fundación Española de Reumatología to I. Ferraz-Amaro and by a grant from the Spanish Ministry of Health (Fondo de Investigaciones Sanitarias) to F. Díaz-González (FIS 09/02209). The work performed by M.A. González-Gay has been supported by grants from Fondo de Investigaciones Sanitarias PI06/0024, PS09/00748 and PI12/00060, from the RETICS Program, RD08/0075 and RD12/0009/0013 (RIER) from the Instituto de Salud Carlos III (ISCIII) (Spain).

Competing interests: none declared.

Introduction

There is growing evidence that the proportions and bodily distribution of fat and lean mass have important implications for health. Characteristically, obesity has been shown, in several large, prospective, long-term studies using multivariate analyses, to be an independent risk factor for all-cause mortality in both women and men (1). Obesity may also promote preclinical atherosclerotic changes by a direct effect on vascular physiology (2). In this context, the American Heart Association has also identified obesity as an independent risk factor for coronary heart disease (CHD) based upon many studies that have demonstrated a linear, longitudinal relationship between obesity and CHD (3, 4). Other studies have demonstrated that central adiposity and total body fat mass are also associated with an increased risk of morbidity and mortality (5, 6). For example, at any given level of body mass index (BMI), the risk of developing cardiovascular disease in both men and women increases with higher levels of abdominal fat (7). For this reason, and due to the fact that body fat can differ dramatically at the same BMI, it is becoming of increasing interest to measure the proportions and patterns of body fat distribution as a more accurate way to quantify its relation with cardiovascular risk. On the other hand, the loss of skeletal muscle mass and strength, a process known as sarcopenia, has been associated with a number of adverse health outcomes, including functional decline, insulin resistance, fatigue, fractures and mortality (8). Although less studied than obesity, sarcopenia has been linked to atherosclerosis as well (9).

Rheumatoid arthritis (RA) is a debilitating, chronic, systemic, autoimmune disease of unknown etiology that causes the destruction of joint cartilage. All-cause mortality is two to five times higher in RA patients than in the general population and the most frequent cause of death in RA is cardiovascular disease (10, 11). Patients with RA have been described as expressing an altered body composition, specifically a decreased fat free mass (FFM), known as 'rheumatoid cachexia'(12), although recent studies have also shown that a substantial portion of individuals with RA may be obese or "overfat" (13-15). This altered body composition in conjunction with a chronic proinflammatory state and combined with additional factors that often occur in patients with RA (*e.g.* low physical activity, joint stiffness, metabolic changes, treatments with corticoids and non-steroidal anti-inflammatory drugs, pain and disuse of muscles) all contribute to the accelerated atherosclerosis observed in patients with RA (16-18). However, this apparent relationship between altered body composition and cardiovascular disease has not been completely elucidated in RA patients.

In this study, we assessed body composition by dual x-ray absorptiometry, abdominal adiposity by magnetic resonance imaging, and the presence of subclinical atherosclerosis by flow-mediated vasodilatation of brachial artery in RA patients and matched controls with no previous history of cardiovascular events. We sought to determine whether body composition and abdominal adiposity are associated with endothelial dysfunction in patients with RA.

Materials and methods

Study participants

One hundred and ninety-seven women, 100 RA patients and 97 age-matched controls, were recruited for this case and control study. Since RA is more prevalent in women and because body phenotypes are related to gender, only women were selected for our study. All RA patients were women 18 years old or older who fulfilled the 2010 ACR/EULAR diagnostic criteria (19). For the purpose of inclusion in the present study, RA disease duration was required to be ≥1 year. Because anti-TNF-alpha treatment has been associated with changes in body fat mass and with improvement in endothelial function (20-22), RA patients undergoing TNF-alpha antagonist therapy were not included in the present study. The control group consisted of people living in the same area during the same time period of the study, and who matched for age and the presence of diabetes, hypertension or smoking. Patients and

controls were excluded if they had a history of myocardial infarction, angina, stroke, a glomerular filtration rate <60 ml/min/1.73 m^2, a history of cancer, or evidence of active infection. None of the controls was receiving glucocorticoids, however, since such anti-inflammatories are often used in the management of RA, patients taking prednisone or an equivalent dose (<10 mg/day or less) were not excluded. The study protocol was approved by the Institutional Review Committee at Hospital Universitario de Canarias (Spain), and all subjects provided written informed consent.

Data collection

Surveys on RA patients and controls were performed in the same way, except for additional questions asked of the former. Subjects completed a cardiovascular risk factor and medication use questionnaire and underwent a physical examination to determine their anthropometrics and blood pressure. Medical records were reviewed to ascertain specific diagnoses and medications. Experienced research nurses obtained all anthropometric measures. In patients with RA, disease activity was measured using the Disease Activity Score (DAS28) in 28 joints (23), while disease disability was determined using the Health Assessment Questionnaire (HAQ) (24).

Abdominal adiposity

Abdominal fat distribution was determined via magnetic resonance imaging (MRI) by estimating subcutaneous and visceral fat in terms of mm^2 area at the baseline visit. Contiguous T1 weighted magnetic resonance images were obtained from the diaphragm to the pubic symphysis using a General Electric 1.5 Tesla Magneto Signa Horizon. The field of view was made large enough to display the entire outline of the abdomen. From this data set, the image closest to the level of the umbilicus was selected for further analysis. This image was transferred to a standalone workstation where images were analysed by an experienced radiologist who was blinded with regard to the clinical characteristics of the participants. Cross-sectional areas of intra-abdominal (IAAT) and subcutaneous abdominal adipose tissue (SAAT) were calculated by identifying and excluding muscle, bone, blood vessels, and gastrointestinal structures (25).

Body composition, obesity and sarcopenia assessments

Body composition and regional body fat distribution were assessed using a Lunar Prodigy DXA system. DXA has been validated as a method of assessing body composition in both younger and older persons. DEXA has been generally accepted as a reproducible method and is sensitive to small changes in body composition (26, 27). BMI was calculated as weight (kg) divided by height (m^2) (28). Obesity by BMI was defined as a BMI ≥30 kg/m^2. With regard to waist circumference (WC), women with a WC ≥88 cm where classified as obese (28). Since there is no unanimous consensus on the standard definition of obesity based on the percentage of body fat, we used the approach put forward by Gallagher *et al*. (29). This formula is based on sex, ethnicity, and age cut-off points vis-à-vis body fat percentages from a large cohort of healthy adults. For the women included in our study (Caucasians), obesity definitions ranged from 21% fat mass in 20-39 year-olds and BMIs <18.5, to 43% fat mass in 60-79 year-olds and BMIs ≥30. Cut-off points for defining sarcopenia were based on the criteria proposed by Jansseen *et al*. (30), which classified *moderate* sarcopenia as a relative skeletal muscle index between 5.76-6.75 kg/m^2, and *high* sarcopenia as ≤5.75 kg/m^2.

Assessment of flow-mediated endothelial-dependent vasodilation of the brachial artery

Flow-mediated endothelium-dependent vasodilatation (FMD) of the brachial artery was assessed by means of ultrasound imaging using a 7-MHz linear probe and automated vessel-diameter measurements (Medical Imaging Applications) as previously described (31). Patients fasted for 8 h before the study and all vasoactive medications were withheld for at least four half-lives. In addition, subjects did not exercise or ingest substances that might affect FMD. The brachial artery was imaged above the antecubital fossa continuously for 1 minute at baseline and again after inflation (pressure, 250 mm Hg for 5 minutes) and deflation of a sphygmomanometer cuff placed on the forearm. Images were subsequently analysed offline with the use of dedicated edge detection software (Brachial Tools, Version 3.2.6, Medical Imaging Applications, Coralville, Iowa). Dilatation was quantified as the change, expressed as a percentage, from baseline to the peak diameter, between 45 and 75 seconds after release of the blood-pressure cuff. After 10 minutes of rest, endothelium-independent dilatation was measured after sublingual administration of 25 μg of nitroglycerin according to the same recording protocol.

Statistical analysis

As we had found in a preliminary study that age accounts for 8% (r=0.08) of the variability observed in endothelial dysfunction, we utilised a model of explanatory regression, adjusted for age, to analyse the relationship between body fat mass and endothelial dysfunction. Taking into account the addition of body fat percentage to the model with the goal of explaining 15% of the observed variability, we recruited 100 patients with RA. To maintain a 1:1 ratio with controls, we similarly included 97 control subjects. Demographic and clinical characteristics shown in Table I were compared between RA patients and controls by using chi2 tests for categorical variables or Student *t*-tests for continuous variables (data described as mean ± standard deviation). For non-continuous variables, either a Mann-Whitney U-test was performed or a logarithmic transformation was made, and data were expressed as a median (interquartile range). An examination of the relationship between body fat composition and endothelial function was carried out using multivariate analysis, adjusting for factors known to be associated with cardiovascular disease (model 1, shown in Table III) or with both these and those related to rheumatoid arthritis (model 1 + model 2, also shown in Table III). Linear trends as

revealed by FMD activity through sarcopenia stratification were tested using linear regression with orthogonal polynomial contrasts. All analyses used a 5% two-sided significance level and were performed using SPSS software, version 21 (IBM, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Results

Demographic, analytical and disease-related data

A total of 197 female participants, 100 RA patients and 97 controls, with a mean (± standard deviation- SD) age of 55.6±9.3 years and 54.8±10.2 years (p=0.57), respectively, were included in this study. Demographic and disease-related characteristics of the participants are shown in Table I. No differences were found between patients and controls regarding BMI, waist and hip circumferences, waist-to-hip ratio and bicipital circumference. There were no differences in the frequency of hypertension and diabetes between patients and controls. RA patients had moderately active disease as shown by DAS28 (3.6±1.0) and displayed a median HAQ of 0.934 (interquartile range, 0.300–1.500). Almost half of them (46.0%) were taking prednisone (mean current dose 2 [0–5] mg/day). Analyses of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values revealed a non-statistically significant trend that was higher in patients than in controls. Lipid profiles did not display differences between patients and controls. FMD was higher in controls compared to RA patients (8.5 [4.5–15.6] % *vs*. 5.3 [0.0–9.2] %, p=0.00) but nitroglycerin mediated dilatation was not different between them.

Table I. Demographic, laboratory and disease-related data.

	Control patients (n=97)	RA patients (n=100)	*p*
Age, years	54.8 ± 10.2	55.6 ± 9.3	0.57
Anthropometric data			
Height, cm	159 ± 7	159 ± 6	0.97
Weight, kg	72 ± 14	74 ± 15	0.31
Body mass index, kg/m^2	28.3 ± 4.9	29.2 ± 5.9	0.21
Waist circumference, cm	94 ± 12	97 ± 16	0.08
Waist/hip ratio	0.88 (0.83-0.91)	0.90 (0.84-0.95)	0.11
Hip circumference, cm	107 ± 12	108 ± 13	0.54
Bicipital circumference, cm	30 ± 5	30 ± 3	0.88
Comorbidities			
Hypertension, n (%)	31 (32)	40 (40)	0.22
Systolic pressure, mmHg	120 (110-140)	121 (114-140)	0.68
Diastolic pressure, mmHg	77 (70-80)	79 (70-81)	0.48
Current smoker, n (%)	2 (2)	3 (3)	0.99
Diabetes, n (%)	7 (7)	15 (15)	0.09
Currently on aspirin, n (%)	10 (10)	6 (6)	0.27
Other chronic illnesses, n (%)	28 (30)	16 (6)	0.03
Laboratory data			
ESR, mm/h	23 (16-39)	25 ± 14	0.10
CRP, mg/L	2.50 (1.20-7.20)	4.13 ± 3.10	0.08
Cholesterol, mg/dL	205 ± 37	214 ± 42	0.29
Triglycerides, mg/dL	106 ± 46	133 ± 77	0.07
HDL cholesterol, mg/dL	54 ± 10	55 ± 14	0.87
LDL cholesterol, mg/dL	130 ± 33	133 ± 35	0.69
Apoliprotein A1, mg/dL	152 ± 16	156 ± 25	0.65
Apoliprotein B, mg/dL	87 ± 28	91 ± 18	0.60
Brachial ecography			
FMD%	8.5 (4.5-15.6)	5.3 (0.0-9.2)	0.00
Rheumatoid arthritis-related data			
DAS28		3.6 ± 1.0	
HAQ		0.934 (0.300-1.500)	
Current prednisone intake, n (%)		46 (46)	
Current prednisone, mg/day		2 (0-5)	
Disease duration, years		9.3 (3.0-13.0)	
Rheumatoid factor, n (%)		53 (53)	
Methotrexate, n (%)		80 (80)	

Values are mean ± standard deviation or median (interquartile range).
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FMD: Flow mediated dilatation.

Body composition and abdominal adiposity as assessed by DEXA and MRI in controls and patients

RA patients, more than controls, tended to conform to the definition of obesity based on BMI (44% *vs*. 33%, p=0.08). There were no differences between controls and patients using the definition of obesity based on waist circumference (68 *vs*. 69%, p=0.86, respectively). Fat-mass index tended to be higher in patients than controls (12907±4215 *vs*. 12336±3563 mg, p=0.32), although this difference did not reach statistical significance. Appendicular-to-total lean mass ratio (0.4±0.02 *vs*. 0.40±0.03, p=0.00) and appendicular-to-trunk lean mass (0.82±0.08 *vs*. 0.78±0.08, p=0.00) were significantly lower in RA patients than in controls. Visceral and parietal abdominal tissue areas (and the ratio between them), as assessed by MRI, did not differ between RA patients and controls (Table II). When obese and sarcopenia phenotypes where analysed, we found that obesity was very frequent in both RA and controls (more than 90% in each group). Elevated sarcopenia, according to the definition put forward by Janssen *et al*., tended to be higher in RA patients than in controls (13% *vs*. 6%, p=0.06). However, this was not the case for individuals included in the categories of moderate or absent sarcopenia, as no differences between patients and controls were found in either category.

The relationship of fat and lean mass to endothelial function in patients and controls

Table III and Figure 1 show the correlations of fat and lean mass indexes and phenotypes with sarcopenia with FMD in RA patients and controls. BMI and waist circumference were not associ-

Table II. Differences in body composition (DEXA) and abdominal adiposity (magnetic resonance image) between controls and patients.

	Controls	RA patients	p^*
Body mass index, kg/m²			
Normal weight, n (%)	24 (25)	28 (28)	0.53
Overweight, n (%)	41 (42)	28 (28)	0.06
Obese, n (%)	32 (33)	44 (44)	0.08
Wais circumference			
Waist circumference >88 cm, n (%)	67 (69)	68 (68)	0.86
DEXA			
Indixes and ratios			
Fat mass index	12336 ± 3563	12907 ± 4215	0.32
Fat-free mass index	15867 ± 1965	16300 ± 2126	0.15
Lean mass index	14904 ± 1899	15386 ± 2074	0.10
% Trunk fat / % Leg fat	1.00 ± 0.12	1.00 ± 0.16	0.91
Apendicular fat mass / m²	5308 ± 1569	5465 ± 1919	0.54
Apendicular lean mass / m²	6182 ± 795	6185 ± 940	0.98
Apendicular / total lean mass	0.42 ± 0.02	0.40 ± 0.03	0.00
Apendicular / total fat mass	0.43 ± 0.05	0.43 ± 0.06	0.56
Appendicular / trunk lean mass	0.82 ± 0.08	0.78 ± 0.08	0.00
Appendicular / trunk fat mass	0.82 ± 0.17	0.81 ± 0.21	0.82
Magnetic resonance imaging			
Visceral abdominal tissue (cm²)	31947 ± 11831	33158 ± 12478	0.55
Subcutaneous abdominal tissue (cm²)	10059 ± 4955	10416 ± 5785	0.69
VAAT/SAAT ratio	0.32 ± 0.14	0.33 ± 0.20	0.74
Phenotypes			
Obese according to Gallagher *et al*., n (%)	87 (90)	91 (91)	0.95
Sarcopenia according to Janssen *et al*.			
High sarcopenia, n (%)	6 (6)	13 (13)	0.06
Moderate sarcopenia, n (%)	36 (37)	37 (37)	0.94
No sarcopenia, n (%)	58 (60)	50 (50)	0.45

Data were expressed as n (%) or media ± standard deviation. Fat mass index: fat mass mg/m²; Fat-free mass index: fat-free mass mg/m²; Lean mass index: lean mass mg/m².
*Data were adjusted for age and comorbidity. VAAT/SAAT: visceral/subcutaneous abdominal adipose tissue ratio.

ated with endothelial function in RA patients or control subjects. When fat mass index was examined in this same regard, the index showed a negative association (per standard deviation -SD-) with FMD in controls after adjusting for age, hypertension, diabetes, and smoking (beta coef. -0.45 [-1.05–0.05], p=0.03). However, this association was not found in RA patients even after adjusting for comorbidity (diabetes, hypertension and smoking) or RA-related covariables. Similarly, 'overfat'– based on the Gallagher definition – showed a trend towards lower FMD values in controls (beta coef. -0.81 [-1.73–0.00], p=0.05), but not in RA patients (beta coef. -0.09 [-0.81–0.64], p=0.81). Lean mass index (per SD) was not associated with FMD in either RA patients or controls. Visceral abdominal fat (per SD) was associated with lower FMD values (beta coef. -0.60 [-1.18–0.02], p=0.04) in controls after adjusting for hypertension, diabetes or smoking. This association was not observed in RA patients even after adjusting for covariates related to the disease such as disease duration and activity, CRP or the presence of rheumatoid factor. Subcutaneous abdominal fat and visceral/subcutaneous adipose tissue ratio similarly had no apparent impact on controls or RA patients.

On the other hand, the relationship of sarcopenia with FMD revealed some similarities between RA patients and controls. In this regard, the presence of high and moderate sarcopenia was associated with lower FMD levels, even adjusting for cardiovascular risk factors and RA-related covariables. Statistical trend analysis confirmed this association (Fig. 1).

Discussion

In our study, we have found that endothelial dysfunction in patients with RA is not associated with total body adiposity and/or visceral abdominal fat. This was not the case with controls where low values of FMD were inversely associated with body adiposity and visceral abdominal fat. Nevertheless, the sarcopenia pheno-

Table III. Multivariable-adjusted linear regression models assessing association of adiposity phenotypes to endothelial dysfunction in RA patients and controls.

	log Flow mediated dilation beta coef (95% CI)									
	RA patients						Controls			
	Unadjusted	p	Model 1	p	Model 2	p	Unadjusted	p	Model 1	p
BMI (kg/m²), per SD	-0.01 (-0.31-0.29)	0.97	-0.07 (-0.53-0.40)	0.77	-0.07 (-0.41-0.28)	0.70	-0.12 (-0.61-0.37)	0.62	0.09 (-0.26-0.43)	0.62
Waist circumference >88 cm	-0.23 (-0.88-0.42)	0.48	-0.07 (-0.80-0.66)	0.85	-0.14 (-0.88-0.61)	0.71	-0.34 (-1.22-0.54)	0.44	-0.38 (-1.23-0.48)	0.37
Overfat Gallagher definition	-0.04 (-0.67-0.59)	0.90	0.17 (-0.54-0.88)	0.62	-0.09 (-0.81-0.64)	0.81	-0.47 (-1.42-0.47)	0.32	-0.81 (-1.73-0.00)	0.05
Fat mass index (fat mass/kg²), per SD	0.15 (-0.57-0.27)	0.47	-0.07 (-0.55-0.41)	0.77	-0.23 (-0.77-0.33)	0.41	-0.40 (-1.02-0.21)	0.19	-0.45 (-1.05--0.05)	0.03
Lean mass index (lean mass/kg²), per SD	-0.10 (-0.42-0.22)	0.55	-1.30 (-0.46-0.20)	0.43	-010 (-0.45-0.26)	0.58	0.24 (-0.54-1.03)	0.54	-0.11 (-0.95-0.73)	0.78
Visceral abdominal fat*, per SD	0.04 (-0.33-0.41)	0.83	0.21 (-0.22-0.64)	0.34	-0.01 (-0.56-0.54)	0.97	-0.63 (-1.25--0.01)	0.04	-0.60 (-1.18--0.02)	0.04
Subcutaneous abdominal fat*, per SD	-0.20 (-0.57-0.18)	0.30	-0.16 (-0.57-0.25)	0.43	-0.30 (-0.76-0.17)	0.20	-0.13 (-0.78-0.51)	0.67	-0.11 (-0.72-0.51)	0.73
VAF/SAF ratio*	0.06 (-0.33-0.44)	0.77	0.12 (-0.29-0.53)	0.54	0.02 (-0.47-0.50)	0.95	-0.41 (-1.06-0.24)	0.20	-0.30 (-0.96-0.35)	0.34

Model 1 is adjusted for age, hypertension, diabetes, smoking and comorbidity. Model 2 is adjusted for all covariates from Model 1 plus disease duration, rheumatoid factor, corticoids intake, C-reactive protein and DAS28. *By magnetic resonance imaging.

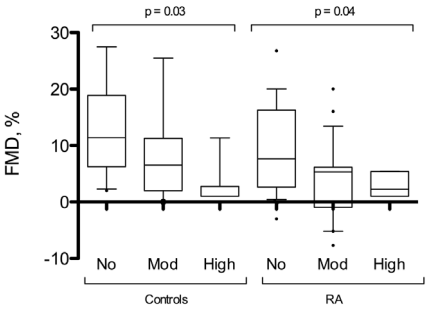

Fig. 1.

type (low lean mass) appeared to be related to endothelial dysfunction in both RA patients and controls. Based on these findings, we hypothesise that endothelial dysfunction in RA patients occurs independently of adiposity, a well-established cardiovascular risk factor prevalent in the general population. Our results suggest that the roles played by fat mass and adiposity may be less relevant in the increased risk levels for cardiovascular disease observed in RA patients *versus* the general population. This finding supports the role of inflammation as a major factor in the development of accelerated atherosclerosis in RA.

Our data regarding body composition are in keeping with prior reports that demonstrated significantly higher proportion of unhealthy body composition phenotypes in patients with RA (13, 32-36). In general, these studies reported a higher total and truncal fat mass, as well as a lower appendicular lean mass, in RA patients compared to controls. Although in our own series RA patients tended to have a higher proportion of fat mass, as well as an increased percentage of sarcopenia than controls, no statistically significant differences were found. Therefore, it is our contention that obesity may have been overestimated in our cohort since its prevalence (and that of overweight) in the Canary Islands is high (37). On the other hand, our study was not designed to identify potential differences in body, composition but rather to determine whether there exists a relationship between endothelial function and body measurements in RA patients.

In keeping with the aforementioned findings, our results regarding magnetic resonance imaging of visceral adiposity did not reveal any differences between patients and controls. Our results were contrasted with those previously reported in the study by Giles *et al*. (38), where subcutaneous fat was significantly different in women with RA compared to their control counterparts. As previously discussed, a potential explanation for these differences may stem from the relatively high frequency of obesity among our healthy controls.

FMD values in patients with RA have been found to correlate with biomarker data on endothelial cell activation and with other surrogate markers of subclinical atherosclerosis (39-42). In this regard, the presence of endothelial dysfunction, as assessed by brachial ultrasound, is known to be a marker of subclinical atherosclerotic cardiovascular disease in at-risk patients (43), and has been linked to adiposity and weight gain in non-rheumatic individuals (44). To the best of our knowledge, however, there is little information regarding the relationship of body composition with a surrogate marker of subclinical cardiovascular disease in patients with RA. In this respect, Dessein *et al*. (45) studied the associations of body mass index and waist circumference with high resolution B-mode ultrasound-determined carotid artery atherosclerosis in 203 African women with established RA (108 black and 95 Caucasian). In this study it was concluded that obesity in women with RA from developing groups of black african descent was not translated into atheroma. Similarly, in other report (46) of the same group, waist circumference was not related either with artery intima-media thickness or carotid artery plaque. On the other hand, Inaba *et al*. assessed the presence of body adiposity and determined brachial-ankle pulse wave velocity by dual-energy x-ray absorptiometry and waveform analyser, respectively in 30 patients with RA and 30 controls (47). In their study, which involved a multiple regression analysis encompassing age, systolic blood pressure, and trunk: peripheral fat ratio as independent variables, the latter emerged as an independent factor significantly associated with brachial-ankle pulse wave velocity in RA patients. In our study, which determined body composition by DEXA and abdominal adiposity, we assessed for the first time the potential association of abdominal fat with endothelial dysfunction in RA. Unlike healthy controls, the lack of a link between visceral adiposity and FMD in RA patients is of potential relevance since it supports the contention that factors different from those traditionally associated with atherosclerotic disease in RA may actually play key roles in its pathogenesis. Contrary to our own findings, one recent study found that obesity was associated with worse RA disease outcomes and a higher prevalence of comorbidities. In this study, BMI and obesity conferred independently higher risks of being diagnosed with hypertension, diabetes mellitus, and/or chronic pulmonary disease (48). In addition, BMI and waist circumference were independently associated with angina pectoris, acute myocardial infarction and/or coronary revascularisation (48). It should be noted, however, that in this study obesity was defined by BMI or waist circumference, and no direct vascular measures were performed. In contrast, the absence of any significant correlation between adiposity and endothelial function in the RA patients from our series was established after adjusting for the classic risk factors and also, of note, by using also more accurate methods of measurement such as DEXA and MRI.

Our finding of a link between sarcopenia and endothelial dysfunction in RA patients is similar to those observed in other disorders, as well as in the general population, where the relationship of sarcopenia with cardiovascular disease has been clearly established. In this regard, Alexandersen *et al*. (49) reported a strong and independent inverse association between aortic calcification and peripheral lean mass, even after adjusting for age and body mass index. Kim *et al*. (50), reported that appendicular skeletal muscle mass and visceral abdominal fat ratio (an index of sarcopenic obesity) were independently and negatively associated with metabolic syndrome and arterial stiffness, as determined by brachial-ankle pulse wave velocity. In keeping with these observations, Kohara *et al*. (51) reported that

brachial-ankle pulse wave velocity was higher (after excluding confounding parameters) in subjects with both thigh muscle sarcopenia and visceral obesity than in those with only one abnormality. An exception to that was found in a series of 30 patients with RA (52), a subgroup that did not exhibit significant differences in either the classic or the novel cardiovascular disease risk factors, in the 10-year cardiovascular risk, or in the prevalence of established cardiovascular disease in patients with rheumatoid cachexia compared to RA patients without this condition.

In accordance with other reports (53), we believe that for unknown reasons the increased fat mass ameliorates disease activity such that obese patients with RA may suffer less joint destruction. Thus, obese patients will probably exhibit central adiposity, insulin resistance, metabolic syndrome and other traditional drivers contributing to an increased cardiovascular risk but, paradoxically, a lower cardiovascular-related morbidity than those with RA and classic sarcopenia (54). Therefore, the overall level of cardiovascular risk in an RA patient will reflect the balance between these opposing factors and, based on epidemiological studies, it appears that the dominant factor among these is the effect of disease activity related to inflammation (52).

We acknowledge that some potential limitations may exist in our study. First, due to the characteristics of our population the frequency of obesity in our study was high in both patients and controls. This fact may account for the lower probability of establishing significant differences between the two groups of individuals. Second, overfat and sarcopenia definitions were taken from studies involving non-rheumatic individuals. Due to this, these definitions may not be applicable to patients with RA. Third, some potential confounders such as physical activity, energy intake and expenditure, which may have influenced the association of body composition with FMD, were not assessed in the present study.

In conclusion, in our population, adiposity does not explain the development of endothelial dysfunction in patients with RA. Nevertheless, sarcopenia was linked to endothelial dysfunction in both healthy controls and patients. Although the actual effects of adiposity and sarcopenia in the development of endothelial dysfunction in patients with chronic inflammatory diseases like RA warrant further investigation, our data may help to establish the influence of body composition or adiposity on the mechanisms associated with cardiovascular disease in RA patients.

References

1. POIRIER P, GILES TD, BRAY GA *et al*.: Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006; 113: 898-918.
2. BEHN A, UR E: The obesity epidemic and its cardiovascular consequences. *Curr Opin Cardiol* 2006; 21: 353-60.
3. WORMSER D, KAPTOGE S, DI ANGELANTONIO E *et al*.: Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; 377: 1085-95.
4. JOUSILAHTI P, TUOMILEHTO J, VARTIAINEN E, PEKKANEN J, PUSKA P: Body weight, cardiovascular risk factors, and coronary mortality. 15-year follow-up of middle-aged men and women in eastern Finland. *Circulation* 1996; 93: 1372-9.
5. JANSSEN I, KATZMARZYK PT, ROSS R: Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004; 79: 379-84.
6. SIMPSON JA, MACINNIS RJ, PEETERS A, HOPPER JL, GILES GG, ENGLISH DR: A comparison of adiposity measures as predictors of all-cause mortality: the Melbourne Collaborative Cohort Study. *Obesity* (Silver Spring). 2007; 15: 994-1003.
7. SNIJDER MB, VAN DAM RM, VISSER M, SEIDELL JC: What aspects of body fat are particularly hazardous and how do we measure them? *Int J Epidemiol* 2006; 35: 83-92.
8. WALSTON JD: Sarcopenia in older adults. *Curr Opin Rheumatol* 2012; 24: 623-7.
9. LIM S, KIM JH, YOON JW *et al*.: Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). *Diabetes Care* 2010; 33: 1652-4.
10. MEUNE C, TOUZE E, TRINQUART L, ALLANORE Y: Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* (Oxford) 2009; 48: 1309-13.
11. AVINA-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.
12. WALSMITH J, ROUBENOFF R: Cachexia in rheumatoid arthritis. *Int J Cardiol* 2002; 85: 89-99.
13. STAVROPOULOS-KALINOGLOU A, METSIOS GS, KOUTEDAKIS Y, KITAS GD: Obesity in rheumatoid arthritis. *Rheumatology* (Oxford) 2011; 50: 450-62.
14. GILES JT, LING SM, FERRUCCI L *et al*.: Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. A*rthritis Rheum* 2008; 59: 807-15.
15. STAVROPOULOS-KALINOGLOU A, METSIOS GS, KOUTEDAKIS Y *et al*.: Redefining overweight and obesity in rheumatoid arthritis patients. *Ann Rheum Dis* 2007; 66: 1316-21.
16. ENGVALL IL, ELKAN AC, TENGSTRAND B, CEDERHOLM T, BRISMAR K, HAFSTROM I: Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. *Scand J Rheumatol* 2008; 37: 321-8.
17. RALL LC, ROUBENOFF R: Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology* (Oxford) 2004; 43: 1219-23.
18. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, MARTIN J: Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; 35: 8-17.
19. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
20. ENGVALL IL, TENGSTRAND B, BRISMAR K, HAFSTROM I: Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomised study over 21 months. *Arthritis Res Ther* 2010; 12: R197.
21. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C: Rheumatoid arthritis: Obesity impairs efficacy of anti-TNF therapy in patients with RA. *Nat Rev Rheumatol* 2012; 8: 641-2.
22. FERRAZ-AMARO I, ARCE-FRANCO M, MUNIZ J *et al*.: Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Horm Metab Res* 2011; 43: 801-8.
23. 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.
24. PINCUS T, SWEARINGEN C, WOLFE F: Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. *Arthritis Rheum* 1999; 42: 2220-30.
25. THOMAS EL, SAEED N, HAJNAL JV *et al*.: Magnetic resonance imaging of total body fat. *J Appl Physiol* 1998; 85: 1778-85.

26. WANG J, HEYMSFIELD SB, AULET M, THORNTON JC, PIERSON RN, JR.: Body fat from body density: underwater weighing vs. dual-photon absorptiometry. *Am J Physiol* 1989; 256: E829-34.
27. VISSER M, PAHOR M, TYLAVSKY F *et al*.: One- and two-year change in body composition as measured by DXA in a population-based cohort of older men and women. *J Appl Physiol* 2003; 94: 2368-74.
28. OBESITY: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; 894: i-xii, 1-253.
29. GALLAGHER D, HEYMSFIELD SB, HEO M, JEBB SA, MURGATROYD PR, SAKAMOTO Y: Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr* 2000; 72: 694-701.
30. JANSSEN I, BAUMGARTNER RN, ROSS R, ROSENBERG IH, ROUBENOFF R: Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol* 2004; 159: 413-21.
31. CORRETTI MC, ANDERSON TJ, BENJAMIN EJ *et al*.: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002; 39: 257-65.
32. DAO HH, DO QT, SAKAMOTO J: Abnormal body composition phenotypes in Vietnamese women with early rheumatoid arthritis. *Rheumatology* (Oxford) 2011; 50: 1250-8.
33. BOOK C, KARLSSON MK, NILSSON JA, AKESSON K, JACOBSSON LT: Changes in body composition after 2 years with rheumatoid arthritis. *Scand J Rheumatol* 2011; 40: 95-100.
34. ELKAN AC, ENGVALL IL, CEDERHOLM T, HAFSTROM I: Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. *Eur J Nutr* 2009; 48: 315-22.
35. GILES JT, BARTLETT SJ, ANDERSEN RE, FONTAINE KR, BATHON JM: Association of body composition with disability in rheumatoid arthritis: impact of appendicular fat and lean tissue mass. *Arthritis Rheum* 2008; 59: 1407-15.
36. SUMMERS GD, DEIGHTON CM, RENNIE MJ, BOOTH AH: Rheumatoid cachexia: a clinical perspective. *Rheumatology* (Oxford) 2008; 47: 1124-31.
37. BAUTISTA-CASTANO I, ALEMAN-PEREZ N, GARCIA-SALVADOR JJ, GONZALEZ-QUESADA A, GARCIA-HERNANDEZ JA, SERRA-MAJEM L: [Prevalence of obesity in pregnant women of Canary Islands, Spain]. *Med Clin* (Barc) 2011; 136: 478-80.
38. GILES JT, ALLISON M, BLUMENTHAL RS *et al*.: Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. *Arthritis Rheum* 2010; 62: 3173-82.
39. SODERGREN A, KARP K, BOMAN K *et al*.: Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima media thickness. *Arthritis Res Ther* 2010; 12: R158.
40. GONZALEZ-JUANATEY C, LLORCA J, GONZALEZ-GAY MA: Correlation between endothelial function and carotid atherosclerosis in rheumatoid arthritis patients with long-standing disease. *Arthritis Res Ther* 2011; 13: R101.
41. DESSEIN PH, TOBIAS M, VELLER MG: Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2006; 33: 2425-32.
42. CHUNG CP, OESER A, SOLUS JF *et al*.: Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis* 2008; 196: 756-63.
43. HALCOX JP, DONALD AE, ELLINS E *et al*.: Endothelial function predicts progression of carotid intima-media thickness. *Circulation* 2009; 119: 1005-12.
44. ROMERO-CORRAL A, SERT-KUNIYOSHI FH, SIERRA-JOHNSON J *et al*.: Modest visceral fat gain causes endothelial dysfunction in healthy humans. *J Am Coll Cardiol* 2010; 56: 662-6.
45. SOLOMON A, NORTON GR, WOODIWISS AJ, DESSEIN PH: Obesity and carotid atherosclerosis in African black and Caucasian women with established rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther* 2012; 14: R67.
46. DESSEIN PH, NORTON GR, JOFFE BI, ABDOOL-CARRIM AT, WOODIWISS AJ, SOLOMON A: Metabolic cardiovascular risk burden and atherosclerosis in African black and Caucasian women with rheumatoid arthritis: a cross-sectional study. *Clin Exp Rheumatol* 2013; 31: 53-61.
47. INABA M, TANAKA K, GOTO H *et al*.: Independent association of increased trunk fat with increased arterial stiffening in postmenopausal patients with rheumatoid arthritis. *J Rheumatol* 2007; 34: 290-5.
48. AJEGANOVA S, ANDERSSON ML, HAFSTROM I: Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset. *Arthritis Care Res* (Hoboken) 2013; 65: 78-87.
49. ALEXANDERSEN P, TANKO LB, BAGGER YZ, JESPERSEN J, SKOUBY SO, CHRISTIANSEN C: Associations between aortic calcification and components of body composition in elderly men. *Obesity* (Silver Spring) 2006; 14: 1571-8.
50. KIM TN, PARK MS, LIM KI *et al*.: Skeletal muscle mass to visceral fat area ratio is associated with metabolic syndrome and arterial stiffness: The Korean Sarcopenic Obesity Study (KSOS). *Diabetes Res Clin Pract* 2011; 93: 285-91.
51. KOHARA K, OCHI M, TABARA Y, NAGAI T, IGASE M, MIKI T: Arterial stiffness in sarcopenic visceral obesity in the elderly: J-SHIPP study. *Int J Cardiol* 2012; 158: 146-8.
52. METSIOS GS, STAVROPOULOS-KALINOGLOU A, PANOULAS VF *et al*.: Rheumatoid cachexia and cardiovascular disease. *Clin Exp Rheumatol* 2009; 27: 985-8.
53. KITAS GD, GABRIEL SE: Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. *Ann Rheum Dis* 2011; 70: 8-14.
54. SUMMERS GD, METSIOS GS, STAVROPOULOS-KALINOGLOU A, KITAS GD: Rheumatoid cachexia and cardiovascular disease. *Nat Rev Rheumatol* 2010; 6: 445-51.