Body composition phenotypes in systemic lupus erythematosus and rheumatoid arthritis: a comparative study of Caucasian female patients

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Abstract

Objective

The amount and distribution of fat and lean mass have important implications for health and systemic inflammation may represent a risk for altered body composition. The aim of this study was to analyse whether changes in body composition are similarly associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), two inflammatory conditions of different pathogenesis.

Methods

Body mass index (BMI), waist circumference, fat mass (FM) and fat-free mass (FFM) were measured in 92 women with SLE, 89 with RA and 107 controls. Results were compared among the 3 groups and correlations of FM percentage were explored within SLE and RA.

Results

Abnormal body composition was more frequent in women with SLE and RA than in non-inflammatory controls, despite having a similar BMI. RA diagnosis was significantly associated with overfat (OR=2.782, 95%CI 1.470–5.264; p=0.002) and central obesity (OR=2.998, 95%CI 1.016–8.841; p=0.04), while sarcopenia was more common among SLE (OR=3.003; 95%CI 1.178–7.676; p=0.01). Sarcopenic obesity, i.e. the coexistence of overfat with sarcopenia, was present in 6.5% of SLE and 5.6% of RA women, but no controls. Independent correlations of FM percentage in women with SLE included smoking, disease activity and CRP. In RA, education, disease activity and cumulative corticosteroid dose were identified as independent predictors of FM percentage.

Conclusion

Women with SLE or RA diagnosis are more likely to have abnormal body composition phenotype, with some differences existing between these two conditions. Changes in body composition are partly explained by the inflammatory burden of disease and its treatment.

Key words

obesity, sarcopenia, systemic lupus erythematosus, rheumatoid arthritis, inflammation
Introduction

The amount and distribution of body fat and lean mass have important implications for health. A very low body mass index (BMI) as well as obesity are associated with reduced life expectancy, increased morbidity and poor quality of life (1-4). Not only the amount of fat, but also the distribution of adipose tissue may have detrimental consequences on health. In fact, a disproportionate accumulation of adipose tissue in the abdominal region, which is a key feature of metabolic syndrome, is associated with a prothrombotic and proinflammatory state and confers a higher risk of developing cardiovascular (CV) diseases (5, 6). Additionally, by secreting adipokines, adipose tissue actively participates in the inflammatory process and higher concentrations of inflammatory markers are present in overweight and obese people, as well as in association with metabolic syndrome (3, 7).

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are multisystemic rheumatic diseases that affect joints and muscles, causing pain, disability and increased risk for physical inactivity (8). Patients often require prolonged therapy with corticosteroids which contributes to weight gain (9). Also, the systemic inflammatory nature of these diseases may, per se, represent an additional risk for altered body composition. In fact, in RA both cachexia and excessive fat mass have been identified more frequently than in the general population (10, 11). In the same way, abnormal body composition phenotypes may also be overrepresented among patients with SLE (12, 13), although information regarding this patient group is limited. Moreover, metabolic syndrome was found more commonly in SLE and RA than in controls matched for age and sex (14, 15). Changes in body composition may therefore represent an additional risk for cardiovascular diseases in SLE and RA.

The present work was undertaken to examine whether changes in body composition are similarly associated with SLE and RA, two chronic inflammatory conditions of different pathogenesis, and to what extent the disease characteristics and pharmacotherapy affect the percentage of body fat mass.

Material and methods

Study population

Adult Caucasian women, fulfilling the American College of Rheumatology (ACR) criteria for SLE or for RA and attending the rheumatology clinic at Hospital Garcia de Orta in Almada, Portugal, on a regular basis, were eligible for the study. The control group consisted of women without chronic inflammatory disorders (patients with tendinitis or with low back pain) attending the same clinic. Exclusion criteria were pregnancy, breastfeeding, ethnicity other than Caucasian, functional class IV as defined by the ACR classification of functional status, ischemic heart disease, and impaired renal function (serum creatinine >1.6 mg/dl). The study was approved by the local Ethics Committee and participants provided written informed consent.

Between January and December 2009 a total of 305 women were recruited. Five declined participation and 12 were excluded. The reasons for exclusion were heart disease in 9 cases and renal insufficiency in 3. The final study population comprised 288 women: 92 with SLE, 89 with RA and 107 controls. Demographic and disease characteristics are summarised in Table I.

Participants underwent a structured interview and physical examination performed by the same trained investigators.

Anthropometric and body composition measurements

All assessments were carried out during the morning of the study visit day with participants in the fasting state in order to minimise circadian variations. Standing height (in cm), and body weight (in kg) were measured with patients wearing light clothes and without shoes, and body mass index (BMI) (kg/m²) was calculated. Waist circumference was measured at the end of the normal expiration with a tape placed horizontally midway between the lower edge of the rib cage and the iliac crest, and the mean of two measurements was taken in account. Total fat mass...
Table I. Demographic and clinical characteristics of studied women.

<table>
<thead>
<tr>
<th></th>
<th>SLE (n=92)</th>
<th>RA (n=89)</th>
<th>Controls (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics and lifestyle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>46.8 ± 14.1</td>
<td>49.8 ± 13.8</td>
<td>47.5 ± 13.1</td>
</tr>
<tr>
<td>Menopause (%)</td>
<td>46 (50 %)</td>
<td>51 (57.3 %)</td>
<td>58 (54.2%)</td>
</tr>
<tr>
<td>Education, years</td>
<td>9.3 ± 5.1</td>
<td>8.8 ± 4.8</td>
<td>8.4 ± 5.3</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>13 (14.1 %)</td>
<td>16 (16.9 %)</td>
<td>23 (21.5%)</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>18 (19.6 %)</td>
<td>10 (11.2%)</td>
<td>20 (18.7%)</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8.5 ± 6.9</td>
<td>9.7 ± 7.1</td>
<td>NA</td>
</tr>
<tr>
<td>DAS28</td>
<td>–</td>
<td>4.24 ± 1.3</td>
<td>NA</td>
</tr>
<tr>
<td>SDI</td>
<td>0 [1]</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>HAQ</td>
<td>–</td>
<td>1.16 ± 0.73</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use (%)</td>
<td>52 (56.5%)</td>
<td>46 (51.7%)</td>
<td>NA</td>
</tr>
<tr>
<td>Current daily dose, mg</td>
<td>5 [8.8]</td>
<td>2.5 [5]</td>
<td>NA</td>
</tr>
<tr>
<td>Cumulative dose, g</td>
<td>7.3 [20.7]</td>
<td>7.3 [15]</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data is presented as mean ± standard deviation for normally distributed, median and interquartile range [IQR] for non-normally distributed continuous variables and proportions (%) for categorical variables.

SLEDAI2K: Systemic lupus erythematosus disease activity index 2000; DAS28: Disease activity score; SDI: Systemic lupus international collaborating clinics/ACR damage index; HAQ: Health assessment questionnaire.

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(in kg), percentage of body fat, and fat-free mass (in kg) were obtained by bio-electrical impedance analysis (BIA), using an Omron HBF-510 Full Body Composition analyser. BIA is a simple method for routine clinical use that correlates well with hydrodensitometry body fat analysis and with the “gold-standard” dual-energy x-ray absorptiometry (DXA) measurement (11). Fat mass index (FMI) was calculated by dividing body fat mass by the square of the height (kg/m²) and fat-free mass index (FFMI) by dividing fat-free mass by the square of the height (kg/m²).

Clinical assessment

Socio-demographic data (age, menopausal status, education), health habits (smoking status, physical activity), disease duration, current and past medications and co-morbidities were assessed by patient self-report and information was completed by review of medical records.

SLE disease activity was evaluated using the SLEDAI2K (16), a measure of ongoing disease activity that ranges from 0 to 105. Damage was scored according to the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (17) from 0 to 46. In RA patients 28 joints were examined for tenderness and swelling, and the disease activity score (DAS28) was calculated using ESR. Disease activity was classified as low (DAS28 <3.2), medium (DAS28 3.2–5.1) or high (DAS28 >5.1) (18). Functional status (disability) was evaluated using the Stanford Health Assessment Questionnaire Disability Index (HAQ) (19), a self-administered questionnaire that gives a score range from 0 to 3, with higher scores indicating lower functional capacity. SDI and HAQ were used as surrogate markers of cumulative disease severity. Blood and urine samples were collected and the required tests performed in order to calculate SLE and RA disease activity (complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase, anti-DNA antibody titer, C3 and C4 level and urinalysis).

Definitions

Participants were classified as physically active if the amount of self-reported weekly aerobic exercise during the last 12 months was ≥3 times and ≥30 min per session. Individuals with BMI <18.5 kg/m² were considered underweight, between 18.5 and 24.9 normal, between 25 and 29.9 overweight and with BMI values ≥30 obese. Abdominal obesity was defined in agreement with WHO (20) and IDF (21) population recommended cut-points, which corresponds to a waist circumference ≥80 cm in Caucasian women. Overfat was defined according to total body FM percentage assessed by BIA. Women were considered overfat if their percentage of body fat was superior to 40.01% (22). The cutoff to define sarcopenia was a FFMI ≤2 SD below the mean of a reference Caucasian population (23). On the basis of FM percentage and FFMI participants were categorised into purely obese (overfat), purely sarcopenic, sarcopenic-obese and normal body composition.

Statistical analysis

Anthropometric and body composition parameters of SLE, RA and control women were compared using one-way analysis of variance for normally distributed continuous variables, with post hoc Bonferroni correction. To compare categorical variables Pearson χ² test or Fisher’s exact test were used. The independent association between the inflammatory diseases and body composition phenotype was assessed by multiple logistic regression. The dependent variable “body composition” was dichotomised into normal body composition phenotype or altered body composition (purely obese, purely sarcopenic and sarcopenic-obese) and the diagnosis, as well as potential confounders (age, BMI, current and cumulative corticosteroid dose), were the covariates.

Subsequently, the impact of clinical features and treatment on fat mass percentage was investigated separately among patients with SLE and those with RA by using linear logistic regression. Variables related in univariate analyses to FM percentage at a p-value <0.20 were considered possible predictors and included in the logistic model. Before performing regression analysis FM percentage was logarithmically transformed to obtain normality, as well as disease activity, SDI, corticosteroid dose, and CRP to ensure the normality of the residuals in multiple linear regression. Statistical calculations were performed using SPSS 17.0.
software and a 2-tailed \( p \)-value <0.05 was selected as significant.

**Results**

**Patients’ characteristics**

Patients and controls had similar socio-demographic and lifestyle characteristics, including age (\( p=0.31 \)) and percentage of post-menopausal women (\( p=0.61 \)). SLE and RA women did not differ significantly with regard to disease duration or current corticosteroid use. Overall, 52 (56.5\%) women with SLE and 46 (51.7\%) with RA were on steroids at the time of evaluation. Among those taking steroids, the median daily dose was higher in SLE, but the cumulative corticosteroid dose was comparable in the 2 groups. The proportion of lupus women on antimalarials and on immunosuppressants was 73\% and 33.6\%, respectively. Eighty two RA women were treated with synthetic disease-modifying anti-rheumatic drugs (DMARDs), of which 92.7\% were on methotrexate (MTX); 39.3\% received biologic drugs (DMARDs), of which 92.7\% were on tocilizumab. Two RA women were treated with synthetic DMARDs and on immunosuppressants.

**Anthropometric and body composition measurements**

Table II shows anthropometric and body composition measurements. Patients and controls had comparable mean BMI. Patients with BMI<25 kg/m\(^2\) were younger (\( p<0.001 \)), pre menopause (\( p=0.006 \)), current smokers (\( p=0.04 \)), had higher education level (\( p=0.0001 \)) and more active disease (\( p=0.03 \), compared with those with BMI\(\geq 25 \) kg/m\(^2\). No differences were found regarding physical active persons, disease duration, disease severity, and corticosteroid use or dose. Body fat mass (FM) was significantly higher in women with RA than in non-inflammatory controls across all BMI categories. Within the normal BMI range, SLE women also presented higher amount of FM. RA diagnosis was associated with greater odds of overweight (OR=2.782, 95\%CI 1.470 to 5.264, \( p=0.002 \)). Low FM was exceptional; only 2 individuals in each inflammatory group and no controls had less than 20\% of body fat. The mean value of FFM was similar across the 3 groups. However, significantly more SLE patients were sarcopenic (OR=3.003; 95\%CI 1.178 to 7.676; \( p=0.01 \)). Moreover, 6.5\% of SLE patients, 5.6\% of RA patients but no controls could be classified as sarcopenic obese (\( p=0.03 \)). Compared with the control group, both SLE and RA women were less likely to have normal body composition. The adjusted OR for altered body composition was 2.581 (95\% CI 1.234–5.396, 0.01).
The prevalence of central obesity differed significantly from controls only in RA women. After adjustment for covariates, the risk of central obesity was almost 3 times higher in RA (OR=2.998, 95%CI 1.016–8.841; p=0.04).

The relationships between clinical features and percentage of FM in SLE women are presented in Table III. In univariate analysis there was a significant association of FM percentage with education, smoking, disease activity, damage and CRP. When possible predictors were entered in multiple linear regression analysis, smoking, disease activity and CRP were identified as independent predictors of FM percentage in lupus women.

Table IV shows the relationships between clinical features and percentage of fat mass in RA women. A strong association of education, HAQ and cumulative corticosteroid dose with FM was observed. However, when clinically important and possible predictors were adjusted for, education, disease activity and cumulative corticosteroid dose were identified as independent predictors of FM percentage in RA.

**Discussion**

In this cross-sectional study of women with SLE and RA we explored the relationship between these two inflammatory rheumatic diseases and body composition. As fat mass, lean mass and fat distribution differ among different ethnic groups (24), only Caucasians were included.

The main finding is that Caucasian women with inflammatory rheumatic diseases are more likely to have abnormal body composition phenotype than non-inflammatory controls, with some differences existing between SLE and RA. The amount of body fat is higher in RA women than in controls, regardless of having comparable mean BMI and a similar proportion of overweight and obesity according to the BMI cutoffs. BMI does not discriminate between lean and fat mass, and the cutoff points of BMI for RA patients have been recently challenged (25). In RA, not only the amount of FM, but also the distribution of adipose tissue is altered. Indeed, the prevalence of central obesity is significantly higher in women with RA as compared to the control group. These findings may have important clinical implications as adipose tissue is a major source of adipokines involved in several metabolic and inflammatory processes. Moreover, abdominal obesity is a surrogate marker of visceral fat accumulation (26) and a well documented predictor of cardiovascular events (27). Abdominal obesity is linked to the insulin resistance observed frequently in RA patients (14, 28) and, while the effective control of inflammatory activity improves insulin resistance (29), serum levels of adipokines seem to remain largely independent of short-term RA disease activity control (30, 31).

The mean fat-free mass was similar in our patients with inflammatory diseases and non-inflammatory controls. However, a significantly greater proportion of SLE (17.4%) and RA (10.1%) women could be classified as sarcopenic, as compared with non-inflammatory controls (6.5%). The excessive waste of fat-free mass found in SLE and RA has been attributed to disease activity and decreased physical activity. Additionally, the catabolic effect of high corticosteroid doses (32), such as those used in severe lupus, might have contributed to the more frequently sarcopenia observed in SLE patients. Reduced lean mass in combination with increased fat mass, a condition that is known as obese sarcopenia, was previously reported in older RA patients (10). Yet, we found obese sarcopenia as frequent in SLE (6.5%) as in RA (5.6%) women and absent among controls. In the general population, obese-sarcopenia is found in older people and is associated with worse physical function (33). Controversy exist whether cardiovascular risk is increased in rheumatic patients with sarcopenia (34).

There is a close relationship between body fat and demographic and lifestyle characteristics. Nevertheless, disease activity and pharmacotherapy also affect the percentage of body fat. The percentage of FM is lower in patients with higher disease activity, which may be explained by the catabolic effect of pro-inflammatory cytokines, in particular IL-6 and TNF, inducing weight and appetite loss (35, 36). In fact, despite not having measured cytokine levels, it has been shown that TNF levels are increased in SLE and in RA as compared with controls (37, 38) and there is evidence that an hypermetabolic state is associated with high levels of TNF, IL-1, and very active disease (39, 40). However, similarly to other authors (41), we could not depict an independent effect of TNF inhibition on total fat mass percentage in moderately active RA.

### Table IV. Predictors of FM percentage in women with RA.

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Univariate regression analysis</th>
<th>Multiple regression analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient*</td>
<td>p-value</td>
</tr>
<tr>
<td>Education, years</td>
<td>-0.023 (-0.032 to -0.014)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking, Y/N</td>
<td>-0.126 (-0.236 to 0.010)</td>
<td>0.06</td>
</tr>
<tr>
<td>Physically active, Y/N</td>
<td>-0.029 (-0.193 to 0.136)</td>
<td>0.73</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>0.07 (-0.002 to 0.143)</td>
<td>0.06</td>
</tr>
<tr>
<td>DAS28</td>
<td>-0.022 (-0.062 to 0.018)</td>
<td>0.13</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.089 (0.015 to 0.158)</td>
<td>0.01</td>
</tr>
<tr>
<td>DMARD use, Y/N</td>
<td>-0.151 (-0.342 to 0.040)</td>
<td>0.12</td>
</tr>
<tr>
<td>TNF inhibitors, Y/N</td>
<td>0.096 (-0.007 to 0.198)</td>
<td>0.07</td>
</tr>
<tr>
<td>Log (Current corticosteroid dose)</td>
<td>0.037 (-0.017 to 0.09)</td>
<td>0.17</td>
</tr>
<tr>
<td>Log (Cumulative corticosteroid dose)</td>
<td>0.047 (0.020 to 0.075)</td>
<td>0.001</td>
</tr>
<tr>
<td>Log (CRP)</td>
<td>-0.05 (-0.155 to 0.055)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

FM: Fat mass; DAS28: Disease activity score; HAQ: Health assessment questionnaire; DMARD: Disease-modifying anti-rheumatic drug; TNF: tumour necrosis factor

*Unstandardised coefficients. Multiple linear regression analysis was adjusted for age. The total explained variance of the model is $R^2=0.542$. 

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The relationship of CRP and FM percentage is inverse in lupus patients and independent of SLEDAI. As CRP is not usually increased in active SLE, and no significant correlation could be detected between CRP and SLEDAI (data not shown), this finding may possibly reflect higher CRP levels related to the adipose tissue itself. Current corticosteroid dose was not identified as an independent predictor of FM percentage. Corticosteroids are used in more active disease and, by controlling inflammation, low doses may counterbalance the catabolic effect of pro-inflammatory cytokines.

Surprisingly, the observations on the amount of fat mass not associated with disease duration, disease severity, exercise, DMARD or immunosuppressant use, a finding that deserves further research. A possible explanation relates to the limitations of the cross sectional study design that cannot accurately assess the cumulative effect of disease, medication and exercise over time. Another limitation of the present study is the lack of dietary intake evaluation, a known risk factor for altered body composition in the general population (42). We cannot rule out differences in nutrient intake related to medication or disease activity as decreased appetite and reduced protein intake may occur in highly active disease (41), but is usually normal when disease activity is controlled (39). Additionally, 59.2% of patients were on steroids and even the small mean prednisolone dose could increase appetite. Nevertheless, our study population comprised a wide spectrum of disease activity which might minimise the effect of inflammatory activity on appetite, thus making significant differences in food or nutrient intake between women with inflammatory disease and controls from the same social and cultural background less likely. Another relevant variable in this context is physical activity. Physical activity did not emerge as having a relevant impact on FM. However, 81.5% of patients were sedentary, which means that the physically active group may have been too small to allow detection of a significant effect.

The rationale for a comparative study of two inflammatory rheumatic diseases was based on the assumption that different inflammatory settings could have a diverse effect on the study parameters. Both diseases are associated with altered body composition phenotype, yet some differences could be detected between SLE and RA. While in RA an increase in FM and central obesity prevails, more SLE women presented decreased lean mass. Nevertheless, the independent negative effect of disease activity on body fat mass was similarly observed in both diseases. These findings provide further support to the hypothesis that the alterations in body composition observed in inflammatory rheumatic diseases are partly explained by the inflammatory process itself.

In conclusion, women with SLE and RA exhibit changes in body composition more frequently than non-inflammatory controls, which may, at least in part, be a consequence of the inflammatory burden of the disease and its treatment. BIA and waist circumference are inexpensive and easy to perform assessments that provide important clinical information in SLE and RA patients. Conversely, weight and BMI do not discriminate between fat and fat-free body mass, which makes them less accurate measures for patients with chronic inflammatory rheumatic diseases.

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