Early rheumatoid arthritis and body composition

Christina Book¹, Magnus K. Karlsson², Kristina Akesson² and Lennart T. H. Jacobsson¹

Objectives. RA is associated with joint destruction and cardiovascular diseases (CVDs). Possible predictors for CVD are early changes in body composition. We therefore evaluated whether lean mass of arms and legs (LMAL), total body fat mass (BFM) or truncal fat distribution (TFD) are altered early in RA, and if so, which factors are associated.

Methods. We included 132 RA patients (95 women) with disease duration of <12 months. Disease activity score (DAS28), HAQ, BMI, comorbidity, smoking and medications were recorded. Total and regional lean mass and fat mass were measured with DXA. Data were compared with 132 age- and gender-matched controls, and possibly associated factors were analysed in linear regression models.

Results. LMAL was low in patients for both women and men (P=0.007 and <0.001, respectively). BMI (P=0.012), BFM (P=0.014) and TFD (P<0.001) were higher than expected in RA women. In bivariate analyses, all adjusted for age and current smoking, disease duration was independently associated with low LMAL in women (P=0.021). High BFM was associated with HAQ × disease duration in men (P=0.033) and DAS28 in women (P=0.011). High TFD was associated with a history of diabetes or CVD in men with RA (P=0.005).

Conclusions. Low LMAL, high BFM and high TFD are present in early RA patients. The long-term significant consequences of these abnormalities need to be determined.

Key words: Early rheumatoid arthritis, Body composition, Cardiovascular disease, Lean mass, Fat mass.

Introduction

RA is associated with several long-term consequences such as progressive joint destruction and increased risk of comorbidities, in particular cardiovascular diseases (CVDs) [1]. In addition, RA has also been associated with low bone mineral density (BMD), low total lean body mass and higher truncal fat distribution (TFD) [2–4].

Although the BMI is an established measure of obesity, it does not provide any information on the distribution of adipose tissue, i.e. whether it is mainly localized centrally or peripherally in the arms and legs. By contrast, measurements with total body DXA can distinguish between total body and regional lean mass and total body fat mass (BFM) [5]. Determination of lean mass and fat mass is of clinical importance, because loss of lean mass in the limbs may result in weakness and disability [6, 7], and RA patients with low or normal BMI had more radiographically recognizable progression after 3 years than RA patients with high BMI [8]. Furthermore, RA is associated with an increased risk of CVD in the long term, with changes in the distribution ratio between lean and fat mass as possible contributing factors. A decrease in lean mass and an increase in truncal fat can lead to negative metabolic consequences, including insulin resistance, diabetes and hypertension [9]. With regard to an increase in truncal fat, the INTERHEART study has, for example, shown that waist-to-hip ratio is a stronger predictor for myocardial infarction than BMI [10].

Few studies have evaluated body composition including regional distribution of lean mass and BFM in patients with RA [2–4], and none has specifically studied this in the early stage of RA (disease duration <1 year). However, in one such study, there was no difference in body composition in RA patients with disease duration of <3 years compared with the group with longer disease duration [4]. Westhovens et al. [2] reported in 1997 that lean body mass was lower at all body sites in RA patients and that total and truncal fat mass were greater than in controls. In a recent study, Giles et al. [4] reported that BFM and truncal fat were greater in female RA patients, as was the percentage of patients with sarcopenia, compared with controls. However, in these last studies mentioned, the mean disease duration at evaluation was 12 and 9 years, respectively; hence no study was done in patients with a recent diagnosis of RA.

The present study was designed to determine lean and fat mass distribution in patients with early RA and to identify factors potentially contributing to alterations in body composition.

Methods

Patients and controls

Malmö, Sweden, had a population of ~260,000 inhabitants in 2001. At that time, RA patients were seen either in the rheumatological outpatient clinic at the university hospital or by one of the three rheumatologists in private practice within the city, but closely associated with the hospital unit. All patients with newly diagnosed RA in these settings during 1995–2001 were eligible for the Malmö Early RA Register (MERA). Early DMARD treatment, especially with MTX, was increasingly used towards the end of the study. The frequency of using glucocorticoids in early RA remained stable during the study period [11]. Enrolment criteria were patients satisfying the ACR classifications of 1987 with total disease duration of ≤12 months. In total, 166 patients (117 women and 49 men) agreed to participate by signing a written informed consent, and the study was approved by the local Ethics Committees of Lund University, Sweden.

In 14 patients (six women and eight men), DXA of total body was not done for various reasons, and 20 patients were excluded from the analyses due to a history of chronic lung disease or malignancy (16 women and 4 men). Thus, 95 women and 37 men were included in this observational study. Controls were selected from a previous study aiming at determining normative data for DXA in the city of Malmö based on 324 subjects, of which approximately half were randomly selected from the general population and half were volunteers, mostly hospital employees [12]. From this control group, one subject was randomly picked from each year of age (±2 years). When possible, we matched for current smoking done. Due to the lack of female controls in the age group between 58 and 71 years, controls could be selected several times for patients in this age span,
Early RA and body composition

resulting in 13 subjects being used as controls to more than one patient. Patients and controls were all Caucasians.

Assessments
The baseline assessment included a clinical examination, including swollen joint count (28 joints) and tender joint count (28 joints) made by the same rheumatologist (C.B.) and a questionnaire identifying risk factors for rheumatoid cachexia such as smoking, BMI (weight/height²), menopausal status and medications. Those medications related to treatment of RA, DMARDs and glucocorticoids were specifically recorded.

The patients were also evaluated in terms of disease activity and disability using the disease activity score (DAS28) [13] and HAQ [14], respectively. Pain and general health were measured by a visual analogue scale (VAS). The physician’s global assessment was scored using a Likert scale, where 0 is no disease activity and 4 is maximum disease activity. To adjust for accumulated burden of disease severity and disease activity on the first visit, we calculated HAQ × disease duration and DAS28 × disease duration.

Comorbidity at baseline was assessed retrospectively for the purpose of this study through a structured review of clinical records for pre-specified diagnosed comorbidities during the 5 years preceding inclusion into the study: diabetes, CVD, chronic lung disease and malignancy.

In blood, IgM-RF and anti-cyclic citrullinated peptide (a-CCP) were measured. IgM-RF was classified as either positive or negative, where <21 kIU/l was considered negative. A-CCP (using QUANTA Lite CCP IgG ELISA, INOVA Diagnostics, San Diego, CA, USA) was considered positive when >20 U/l.

Total body scan
Total and regional fat mass and lean mass were measured using DXA (Lunar DPX-L equipment, 1.3z Lunar®, Madison, WI, USA). Fat mass is reported as BFM, truncal fat mass and fat mass of arms and legs, whereas lean mass is reported for total body lean mass and lean mass of arms and legs (LMAL). These values were compared with the same traits in age- and gender-matched subjects measured with the same equipment as part of a previous population-based study of people living in Malmö [12]. The proportion of fat distributed to the trunk was calculated as the fat mass of the trunk divided by the sum of fat mass of arms and legs (TFD). The precision of our DXA apparatus in vivo was evaluated by double measurements after reposition in 14 healthy adults for total body BMD 0.4%, lumbar spine BMD 0.5%, femoral neck BMD 1.6%, BFM 4.1% and total lean mass 0.6%.

Statistical analyses
Cases and matched controls were compared with univariate analysis of variance (ANOVA) analyses taking the matched design into account. In bivariate linear regression models, we evaluated possibly associated factors with LMAL, BFM and TFD. BMI was only evaluated against TFD, due to its obvious strong association with lean body mass and total fat. All analyses were adjusted for current smoking habits and all regression analyses were in addition adjusted for age. To check the assumption for the regression models, residual analyses were performed. Due to the low frequency for diabetes and CVD, they were analysed as whether any comorbidity was present or not. A P-value of <0.05 was considered to indicate a statistically significant difference.

All statistics were calculated using the SPSS version 14.0 for Windows (SPSS, Chicago, IL, USA).

Results
Baseline characteristics
Table 1 shows the baseline clinical characteristics of the 132 RA patients, the use of DMARDs, glucocorticoids and comorbidity and, when applicable, the same characteristics in the controls. The RA women had a mean DAS28 of 4.3 and the RA men 4.5. Fewer (31%) women than men (38%) were using corticosteroids, with a mean daily dosage of 6.5 and 8 mg, respectively. All patients with pre-treatment of corticosteroids or DMARDs had been treated for <30 days. One RA woman had diabetes type II, three had CVD and one woman had both diabetes and CVD. The mean duration of these diseases were 7.5 and 3.6 years, respectively. In the male RA group, one patient had diabetes type II, six patients had CVD and two patients had both diabetes and CVD, with disease duration of 6.8 and 3.4 years, respectively.

The RA women but not men had significant greater weight and BMI than the control group (Table 2).

Body composition
Adjusting for current smoking, women with RA had higher BFM and higher TFD than matched controls (Table 2). By contrast, both women and men with RA had lower LMAL than matched controls. Differences remained significant to a similar degree after additional adjustment for menopausal status (data not shown).

LMAL
In RA patients, adjusting for age and current smoking, disease duration correlated with LMAL but only in women (P = 0.021). Medication or other markers for disease severity were not associated with LMAL. Higher age, unadjusted for other factors, was also associated with lower LMAL in both genders (Table 3).

*A Ninety-five sets of control data from 82 female control subjects. AMA: anti-malarian.
Corticosteroids

Disease duration

BMI, kg/m² 25.1 (24.4, 25.9) 23.7 (23, 24.4) 0.012 25.6 (24.5, 26.7) 26.1 (25, 27.2) 0.501

Weight, kg 68.1 (65.8, 70.3) 64 (61.8, 66.3) 0.016 79.4 (75.6, 83.3) 80.9 (77.1, 84.8) 0.525

Fat mass in women (BMI in women (BMI in men 

In RA patients, adjusting for age and current smoking, there was a significant bivariate correlation between DAS28 and BFM in women (P = 0.011) and between HAQ × duration in men (P = 0.033). Medication or other markers for disease severity were not associated with BFM. Current smoking, unadjusted for other factors, was also associated with higher BFM in female patients (Table 4).

**Total BFM**

In RA patients, adjusting for age and current smoking, BMI in women (P = 0.001) and comorbidity (diabetes or CVD) in men (P = 0.005) were significantly correlated to TFD. Medication or other markers for disease severity were not associated with TFD. Higher age, unadjusted for other factors, was also associated with higher TFD in female patients (Table 5).

**Possible confounders**

The differences between cases and controls in several body composition measures could not be explained by differences in age due to the matched design, and remained significant after adjustment for possible confounders, such as current smoking or menopausal status.
Discussion

In this study, we found that women and men with early RA already had low LMAL at their initial evaluation. For women with early RA we also found higher BMI, BFM and TFD than would be expected based on their age.

There have been few studies concerning body composition in RA patients and the present study is apparently the first to evaluate body composition in early disease. Our results differ slightly from those in a larger US study in later disease [4], in which similar findings were found in both men and women. Both studies used population-based controls but differed significantly with regard to disease duration in patients, which could possibly explain the discrepancies. The mean disease duration in the present study was 7 months, whereas in the US study it was 9 years. In another study with Turkish RA women, in which the mean disease duration was also 9 years, lean body mass and grip strength was less than that in controls [3]. A decrease in lean mass could possibly have multiple unfavourable consequences such as an increased risk for joint destruction, disability, as well as an increased risk for falls and fractures [15]. It is also likely to be associated with a decreased level of exercise due to sarcopenia and could hypothetically lead to increased insulin resistance [16], which could partially explain some of the increased risk of CVD comorbidity in RA.

The higher BFM and TFD in female RA patients were also reported in previous studies of patients with more longstanding disease [2–4]. The high TFD seen in women with RA is a well-known risk factor for CVD morbidity in non-RA patients [17], and it is likely that it could have similar harmful effects in RA patients, possibly partly explaining the well-known increase in CVD in this group [1].

None of the factors was identified as a strong predictor of low LMAL in RA patients in the present study, although the disease duration, possibly reflecting burden of disability, predicted lower values in women. A recently published study on RA patients with a mean disease duration of 12 years, demonstrated significant association between disability as in HAQ and decreasing LMAL, which supports our observations with an association to disease duration [18]. Other possible predictors could be pre-disease body composition and physical activity prior to disease, but we lack information concerning these factors. If these factors were to be able to explain our findings they would, however, need to differ in pre-clinical RA (compared with population-based controls), but these topics have not been studied.

The higher values for BFM found in RA revealed in a similar fashion only modest associations with various markers for disease severity and activity, being significantly associated only with DAS28 in female patients. One reason for these modest associations could be that the burden of disease was insufficiently evaluated by the standard measures used to capture disability and disease activity, i.e. HAQ and DAS28. Other explanations could be factors not measured in our study or that patients already had these abnormalities before disease development. Previous studies have shown that high birth weight is a predictor for adult RA [19, 20], whereas data regarding whether BMI prior to disease differs in RA patients from others are conflicting [21]. This lack of association with markers for disease severity and disease activity is similar to the findings of the study by Westhovens et al. [2], but differs slightly from the findings in the larger study by Giles et al. [4], who found significant associations between altered body composition and HAQ, CRP and RF seropositivity.

Adipose tissue has become an increasingly interesting factor, not only for the development of metabolic syndrome, but also as an important index for the production of factors that may influence the inflammatory response. Adipose tissue is now known to produce pro-inflammatory cytokines, such as TNF-α, IL-6 and adipocytokines, such as adiponectin [22]. Adipocytokines are to some extent responsible for the development of increased insulin resistance and CVD [23, 24]. The relative importance of these adipose tissue-derived factors in RA is still unclear. A recent study found that high BMI protected against development of erosion in patients with undifferentiated polyarthritis [25], but these findings need to be confirmed.

The strengths of this study include that only patients with early disease were evaluated, since this important group has not been previously studied, and that the same equipment and evaluations were used for measuring body composition in both cases and controls. Potential limitations are the relatively small sample size of men, which reduces the possibility for precise evaluation, and the lack of information regarding pre-diagnosis BMI, socioeconomic status, body composition and physical activity. Another limitation is that we only have information on current smoking, and no detailed information concerning previous smoking exposure, and there is no information on the amount smoked.

In conclusion, our results demonstrate that both female and male patients with early RA disease have lower LMAL and a deficit that seems to be higher with increasing age. Women with early RA seem to have higher BFM and a higher proportion of TFD than could be expected by age. This discrepancy in body composition could not be explained by common markers for disease severity and disease activity. Longitudinal studies of this and other cohorts of patients with short disease duration are needed to determine the long-term effects of these modifiable and potentially harmful abnormalities.

TABLE 5. Bivariate correlations and linear regression models of possible predictors of TFD (trunk/arms + legs) in RA patients, adjusted for age and smoking

<table>
<thead>
<tr>
<th>Women (n = 95)</th>
<th>Men (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.057</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>-0.009</td>
</tr>
<tr>
<td>BMI</td>
<td>0.015</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.016</td>
</tr>
<tr>
<td>HAQ × disease duration</td>
<td>0.0002</td>
</tr>
<tr>
<td>DAS28</td>
<td>0.008</td>
</tr>
<tr>
<td>DAS28 × disease duration</td>
<td>-0.001</td>
</tr>
<tr>
<td>IgM-RF positivity</td>
<td>0.113</td>
</tr>
<tr>
<td>a-CCP positivity</td>
<td>-0.016</td>
</tr>
<tr>
<td>a-CCP and IgM-RF positivity</td>
<td>-0.003</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>-0.063</td>
</tr>
<tr>
<td>DMIARs</td>
<td>-0.002</td>
</tr>
<tr>
<td>Diabetes or CVD</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*Unadjusted. B; regression coefficient; r: Pearson’s correlation coefficient.
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References