Chapter 5

The short-term effects of two high-dose, step-down prednisolone regimens on body composition in early rheumatoid arthritis

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**Abstract**

**Objective:** To investigate the effect of two different high-dose, step-down prednisolone regimens on body composition in early RA patients after 26 weeks of treatment.

**Methods:** Prednisolone-naive patients with recent-onset RA (n=108) were randomized to either COBRA (prednisolone 60 mg/day, tapered to 7.5 mg/day in 6 weeks; MTX and SSZ) or COBRA-light therapy (prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX). Body composition was assessed at baseline (before or soon after start of treatment) and after 26 weeks with DXA, and recorded as total body mass (TBM), total fat mass (FM), total lean mass (LM) and trunk/peripheral fat ratio. Log-ratio analyses assessed the proportional distribution of TBM (between LM, FM and bone mass) and FM (between trunk, extremities and head). The subgroup of patients with a DXA before start of treatment (n=38) was analysed separately.

**Results:** In the subgroup of patients with a DXA before start of treatment, TBM increased by 1.6 kg (p<0.001) and total FM by 1.3 kg (p<0.001). The trunk/peripheral fat ratio and the proportional distribution of TBM and FM remained stable over time. There were no differences between the treatment groups. Similar results were obtained in the study population as a whole.

**Conclusion:** Both high-dose, step-down prednisolone regimens caused increases in TBM, mainly caused by an increase in FM, but we found no fat redistribution from peripheral to central tissues. This absence in fat redistribution contradicts the widely held assumption of rapid adverse effects of prednisolone on body composition in RA.
**Introduction**

RA is a chronic, systemic autoimmune disorder characterized by inflammation of the joints, destruction of joint cartilage and bone, and changes in body composition. Chronic, systemic inflammation is associated with changes in cytokine levels that cause hyper-metabolism, followed by an increase in energy demand that causes loss of lean mass (LM).\(^1\)\(^-\)\(^3\) During exacerbations of disease, decreased physical activity and disuse of muscles may lead to a further loss of LM.\(^2\) Decreased LM may decrease functional capacity and has serious consequences for morbidity and mortality of RA patients.\(^1\)\(^-\)\(^3\)

RA patients with decreased LM often demonstrate a concurrent increase in fat mass (FM). This condition, in which loss of LM is compensated by a gain in FM, is called ‘rheumatoid cachexia’.\(^1\)\(^-\)\(^2\) FM, or adipose tissue, is considered to be an active, endocrine organ, secreting several adipokines.\(^4\)\(^-\)\(^5\) Increased FM and obesity are associated with increased risk of hypertension, diabetes mellitus and cardiovascular diseases, also in RA.\(^1\)\(^-\)\(^5\)\(^-\)\(^7\) Individuals with mainly abdominal or central FM are at greater cardiovascular risk than those with mainly peripheral FM.\(^5\)\(^-\)\(^7\) The trunk/peripheral fat ratio (TPFR), a measure of central obesity, is an important predictor of this cardiovascular risk.\(^7\)\(^-\)\(^9\)

Prednisolone, a glucocorticoid (GC), is often used in the initial treatment strategy of RA patients, as it is well-known to reduce inflammation rapidly and effectively. In clinical practice, it is often used as part of combination therapy with other disease-modifying anti-rheumatic drugs (DMARDs).

Combination therapy, including the original COBRA therapy (Dutch acronym for ‘COmbinatietherapie Bij Reumatoïde Artritis’, combination therapy for rheumatoid arthritis) published in 1997\(^10\) and the more recent COBRA-light therapy,\(^11\)\(^-\)\(^12\) has proven to be a successful treatment for early RA, reducing disease activity, limiting radiological progression and improving physical functioning rapidly. Both therapies combine prednisolone and methotrexate (MTX); the COBRA treatment also includes sulfasalazine (SSZ).

Next to its anti-inflammatory properties, prednisolone may cause alterations in energy metabolism, and high doses lead to muscle wasting, fat accumulation and fat redistribution from peripheral to central tissues.\(^13\) Therefore, careful assessment of body composition is important when prescribing prednisolone.

Body Mass Index (BMI) is a simple and easy parameter to assess body composition, however, it fails to identify the loss in LM and gain in FM often present in (weight stable) RA patients.\(^14\)\(^-\)\(^16\) Preferably, both LM and FM components are assessed, which can be done with dual-energy X-ray absorptiometry (DXA), a commonly applied method in clinical studies.\(^1\)

At this moment, the short-term effects of prednisolone on body composition of early, prednisolone- and DMARD-naive, RA patients is unknown. Therefore, our aim was to investigate the effect of two different high-dose, step-down prednisolone regimens on body composition in early RA patients after 26 weeks of treatment.
Patients and methods

Study design and study population
This study was part of the larger multi-centre COBRA-light trial, which assessed the non-inferiority of ‘COBRA-light’ versus COBRA therapy on clinical and radiological outcomes in 164 patients with recent-onset RA at VU University Medical Center (VUmc), Reade and Westfriesgasthuis in The Netherlands.11,12

In brief, COBRA-light therapy (prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX escalated to 25 mg/week in 8 weeks) was compared with COBRA therapy (prednisolone 60 mg/day, tapered to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and SSZ 2 g/day). Patients in the COBRA-light treatment group received a cumulative dose of 1750 mg prednisolone after 26 weeks (mean daily dose: 9.6 mg), and patients in the COBRA treatment group 2275 mg (mean daily dose: 12.5 mg).

Patients previously treated with glucocorticoids or DMARDs other than antimalarial agents were excluded from participation.11 Eligibility criteria, the randomisation process and study design have been reported previously.11

Primary outcome measures of this main study were the Disease Activity Score in 44 joints (DAS), physical functioning assessed with the Dutch consensus version of the Health Assessment Questionnaire (HAQ),17 and radiological damage of both hand and feet, according to the Sharp – van der Heijde Score (SHS) method.18

Ethics committees at each participating centre approved the protocol; patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki/Good Clinical Practice.

It was not possible to perform DXA scans at the Westfriesgasthuis, and patients of this study centre were therefore excluded from analyses (n=29). Patients with a lacking DXA at baseline and/or at 26 weeks (n=26), and with intentional weight loss >10 kg within 26 weeks of treatment (n=1) were also excluded from analyses. Altogether, 108 patients with complete data were included for analyses.

Body composition
To assess BMI, current body weight was measured, without shoes and clothing, to the nearest 0.1 kg on a digital scale (Seca, Hamburg, Germany). Height was also measured, without shoes, to the nearest 0.1 cm. BMI was calculated as ratio weight/height² (kg/m²) and categorized according to the sex independent World Health Organisation categories.19

To assess FM and LM, whole body DXA scans were performed according to the protocol of the manufacturer. Patients of VUmc (n=24) were scanned with the Hologic Delphi (Hologic, Inc; Bedford, Massachusetts, United States), and patients of Reade (n=84) with GE Lunar iDxa (GE Corporate, Madison, Wisconsin, United States).

FM was reported as total FM (sum of trunk, both arms and legs, and head (including neck)), FM on trunk, FM on arms and legs, TPFR (ratio FM on trunk/sum of FM on both
arms and legs) and body fat percentage (ratio total FM/TBM). LM was reported as total LM and LM on arms and legs. Total Body Mass (TBM) is the sum of total FM, total LM and bone mineral content (BMC).

Analysis groups
Due to logistic reasons and our aim to start treatment in early, active RA patients as soon as possible, 65% of the baseline DXA's were performed after patients started their treatment. Therefore, we conducted two separate analyses. In the primary analyses, we included the patients who started treatment after baseline DXA (n=38). In the secondary analyses, we included all patients (n=108): both patients who started treatment before baseline DXA and patients who started treatment soon after baseline DXA.

Statistical analysis
Data are presented as mean (standard deviation), or as median [25th percentile, 75th percentile] in case of skewed data, unless otherwise specified.

If we would have tested all individual body composition parameters for significance, the mutual, proportional and interrelated character of these parameters would be neglected, which likely leads to overanalysis and multiplicity of statistical testing. Therefore, only TBM, total FM and TPFR were tested for significance in this study: two simple and easy interpretable parameters (TBM, FM) and an important predictor of cardiovascular risk (TPFR). These analyses were complemented by log-ratio analyses to evaluate differences in changes in the composition of TBM and distribution of FM over the body.

Differences in changes in TBM, FM and TPFR over time were compared between the treatment groups using a mixed model with fixed effects for time point (0 or 26 weeks), treatment group and their interaction. In case we did not observe a significant treatment group by time interaction, we performed an additional analysis in which we ignored treatment group and tested for a change over time in the total group of (primary analysis) patients using a paired t-test.

Log-ratio analyses, as described by Faes et al., were used to evaluate changes in composition of TBM, given as the proportions LM, FM and BMC of TBM, over time and to evaluate differences in changes in composition of TBM between treatment groups. Log-ratio analysis is suitable for studying trends of multiple relative contributions simultaneously, taking into account that the sum of all contributions must equal 1. We used LM as reference component and calculated separate log-ratios for FM and BMC per patient per time point as \( y = \log(\text{FM}/\text{LM}) = \log(\text{proportion FM/proportion LM}) \) and \( y = \log(\text{proportion BMC/proportion LM}) \). We created a long dataset containing the four log ratios per patient in separate rows and included an indicator variable for time point (0 or 26 weeks) and component (FM or BMC). We fitted mixed models with fixed effects for time (0, 26 weeks), treatment group (COBRA, COBRA-light), component (FM, BMC), and all interactions between these variables. We included a random effect for patient and an
unstructured correlation matrix modelled the correlation between the two log-ratios for FM and BMC for the same patient at the same time. In case we did not observe significant differences in change between treatment groups over time, we ignored treatment group in subsequent analyses in which we tested whether TBM composition changed over time in the total group of (primary analysis) patients. We tested for differences in changes in distribution of total FM over the body (proportion of total FM on trunk, extremities, and head including neck) between the two treatment groups in a similar way.

Due to extreme adiposity, 12 patients (11% of total study population) did not fit completely under the DXA scan. In these cases, one side of the body was accurately measured and the other side of the body was estimated based on this measurement. Sensitivity analyses were performed to compare regular scans with partly estimated scans. All statistical analyses were performed with IBM SPSS Statistics, release 20.0 (SPSS Inc, Chicago, Illinious, United States); p-values<0.05 were considered significant.

## Results

### Study populations

In the primary analysis group, 38 early RA patients (68% women, mean age 51 years) with a baseline DXA before start of treatment were included (Table 1). These patients had a mean DAS of 3.9, a median HAQ of 1.3 and a median SHS of 0.3 at baseline.

In the secondary analysis group, 108 early RA patients (68% women, mean age 53 years) with a baseline DXA before or soon after start of treatment were included. Within this analysis group, 35% of the patients underwent the baseline DXA before start of treatment, 51% within one week after start of treatment, 72% within two weeks, 81% within three weeks and 90% within a month after start of treatment. The patients in this group had a mean DAS of 4.0, a median HAQ of 1.3 and a median SHS of 0 at baseline.

We found no statistically significant differences in patient characteristics between the COBRA and COBRA-light treatment group of both analysis groups at baseline.

### Body mass index

In the primary analysis group, 45% of the patients had a normal BMI at baseline, 45% was overweight, and 10% was obese (Table 2). At 26 weeks, prevalence of normal BMI decreased to 37%, and prevalence of overweight and obesity increased to 50% and 13%, respectively. In the secondary analysis group, a similar trend was shown.
TABLE 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Primary analysis group</th>
<th>Secondary analysis group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>COBRA group (n=20)</td>
<td>COBRA-light group (n=18)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (75)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Age in years</td>
<td>52 (11)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>5 (25)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Disease duration in weeks</td>
<td>17 (10;29)</td>
<td>13 (7;26)</td>
</tr>
<tr>
<td>DAS</td>
<td>4.0 (0.9)</td>
<td>3.9 (0.7)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.3 [1.0;1.6]</td>
<td>1.4 [0.7;1.9]</td>
</tr>
<tr>
<td>SHS</td>
<td>0 [0;1.8]</td>
<td>0.8 [0;3.0]</td>
</tr>
<tr>
<td>Weight in kg</td>
<td>73.1 (10.7)</td>
<td>74.1 (13.5)</td>
</tr>
<tr>
<td>Height in m</td>
<td>1.69 (0.07)</td>
<td>1.71 (0.09)</td>
</tr>
<tr>
<td>Body Mass Index in kg/m²</td>
<td>26.0 [22.5;27.1]</td>
<td>25.2 [21.4;28.6]</td>
</tr>
<tr>
<td>Patient assessment of disease activity</td>
<td>66 [51;77]</td>
<td>69 [50;76]</td>
</tr>
<tr>
<td>Patient assessment of pain</td>
<td>70 [46;81]</td>
<td>55 [33;79]</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>69 [49;86]</td>
<td>64 [45;80]</td>
</tr>
<tr>
<td>Physician assessment of disease activity</td>
<td>46 [38;56]</td>
<td>40 [40;55]</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation) for normally distributed variables and as median [25th percentile;75th percentile] for non-parametric variables, unless otherwise specified; patient and physician assessments by visual analogue scale in mm; there were no statistically significant differences between the COBRA and COBRA-light treatment groups at baseline; DAS = Disease Activity Score of 44 joints, HAQ = Health Assessment Questionnaire, SHS = Sharp - Van der Heijde Score.

TABLE 2. Changes in body mass index after 26 weeks of prednisolone treatment

<table>
<thead>
<tr>
<th></th>
<th>Primary analysis group</th>
<th>Secondary analysis group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COBRA group (n=20)</td>
<td>COBRA-light group (n=18)</td>
</tr>
<tr>
<td>BMI category</td>
<td>Cut of point (kg/m²)</td>
<td>week 0</td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.0</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

Results presented as frequencies (%), BMI = Body Mass Index.

Changes in total body mass

In the primary analysis group, changes in TBM did not differ significantly between both treatment groups, as indicated by a non significant treatment group by time interaction (data not shown). When we analysed data of both treatment groups as one group, TBM increased significantly by 1.6 kg after 26 weeks (p<0.001) (Table 3). In the secondary analysis group, a similar pattern was shown (Table 4).
Sensitivity analyses showed no relevant differences between the results of the regular DXA scans and the estimated DXA scans of the 12 extreme adipose patients for all major body composition analyses in both analysis groups.

**TABLE 3.** Changes in body composition components after 26 weeks of prednisolone treatment in the primary analysis group (n=38)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=38)</th>
<th>COBRA group (n=20)</th>
<th>COBRA-light group (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>week 26</td>
<td>baseline</td>
</tr>
<tr>
<td><strong>Total Body Mass (kg)</strong></td>
<td>73.6 (11.9)</td>
<td>75.2 (12.2)*</td>
<td>73.1 (10.7)</td>
</tr>
<tr>
<td><strong>Fat Mass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- total (kg)</td>
<td>25.0 (9.8)</td>
<td>26.3 (10.3)*</td>
<td>25.3 (8.5)</td>
</tr>
<tr>
<td>- on trunk (kg)</td>
<td>11.1 [7.7;17.1]</td>
<td>12.0 [9.0;17.3]</td>
<td>11.8 [8.7;16.3]</td>
</tr>
<tr>
<td>- trunk/peripheral fat ratio</td>
<td>1.1 (0.4)</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>- body fat %</td>
<td>33.5 (9.2)</td>
<td>34.4 (9.2)</td>
<td>34.2 (8.2)</td>
</tr>
<tr>
<td><strong>Lean Mass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- total (kg)</td>
<td>46.1 (8.7)</td>
<td>46.4 (8.2)</td>
<td>45.4 (7.4)</td>
</tr>
<tr>
<td>- on arms and legs (kg)</td>
<td>20.4 (4.6)</td>
<td>20.5 (4.2)</td>
<td>20.1 (4.1)</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>25.6 (4.5)</td>
<td>26.2 (4.8)</td>
<td>25.6 (3.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation) for normally distributed variables and as median [25th percentile;75th percentile] for non-parametric variables; ¥ only total body mass, total fat mass, and trunk/peripheral fat ratio were tested for significance; * significant change between baseline and week 26 (p<0.05).

**TABLE 4.** Changes in body composition components after 26 weeks of prednisolone treatment in the secondary analysis group (n=108)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=108)</th>
<th>COBRA group (n=54)</th>
<th>COBRA-light group (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>week 26</td>
<td>baseline</td>
</tr>
<tr>
<td><strong>Total Body Mass (kg)</strong></td>
<td>74.8 (14.4)</td>
<td>76.4 (15.0)*</td>
<td>72.9 (12.3)</td>
</tr>
<tr>
<td><strong>Fat Mass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- total (kg)</td>
<td>25.7 (10.5)</td>
<td>27.0 (11.1)*</td>
<td>25.1 (8.5)</td>
</tr>
<tr>
<td>- trunk/peripheral fat ratio</td>
<td>1.1 (0.4)</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>- body fat %</td>
<td>33.9 (9.3)</td>
<td>34.7 (9.4)</td>
<td>34.0 (8.3)</td>
</tr>
<tr>
<td><strong>Lean Mass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- total (kg)</td>
<td>46.6 (9.4)</td>
<td>46.9 (9.2)</td>
<td>45.4 (8.3)</td>
</tr>
<tr>
<td>- on arms and legs (kg)</td>
<td>20.6 (5.1)</td>
<td>20.8 (4.9)</td>
<td>20.0 (4.9)</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>26.2 (5.0)</td>
<td>26.8 (5.3)</td>
<td>25.7 (4.0)</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation) for normally distributed variables and as median [25th percentile;75th percentile] for non-parametric variables; ¥ only total body mass, total fat mass and trunk/peripheral fat ratio were tested for significance; * significant change between baseline and week 26 (p<0.05).
Changes in total fat mass
In the primary analysis group, changes in total FM over time did not differ significantly between both treatment groups. When we analysed data of both treatment groups as one group, total FM increased significantly by 1.3 kg after 26 weeks (p<0.001) (Table 3). In the secondary analysis group a similar pattern was shown (Table 4).

Changes in trunk/peripheral fat ratio
In the primary analysis group, changes in TPFR over time did not differ significantly between both treatment groups. When we analysed data of both treatment groups as one group, TPFR increased by 1% after 26 weeks (p=0.506) (Table 3). In the secondary analysis group, a similar pattern was shown (Table 4).

Changes in composition of TBM: proportion LM, FM and BMC
In the primary analysis group, log-ratio analyses did not demonstrate a significant difference in the longitudinal course of the composition of TBM (LM, FM and BMC proportions) between both treatment groups. When we analysed data of both treatment groups as one group, we found no significant change in the composition of TBM over time (Figure 1). In the secondary analysis group, a similar pattern was shown.

Changes in distribution of FM over the body: proportion on trunk, extremities and head
In the primary analysis group, log-ratio analyses did not demonstrate a significant difference in the longitudinal course of the distribution of FM over trunk, extremities and head between both treatment groups. When we analysed data of both treatment groups as one group, we found no significant change in the distribution of FM over time (Figure 2). In the secondary analysis group, a similar pattern was shown.

FIGURE 1. Changes in total body mass composition after 26 weeks of prednisolone treatment in the primary analysis group (n=38)

FIGURE 2. Changes in fat mass distribution over the body after 26 weeks of prednisolone treatment in the primary analysis group (n=38)
Discussion

This is the first prospective study that investigates the short-term effects of two high-dose, step-down prednisolone regimens on body composition in early RA patients. In this study, GC- and DMARD-naive RA patients increased their TBM and FM after 26 weeks of GC treatment, but more importantly: maintained their TPFR and proportional distribution of TBM and FM.

Earlier studies on side effects of GC’s often focused on the effect on bones, glucose sensitivity, blood pressure and cardiovascular events such as myocardial infarctions and strokes. The original COBRA trial reported a significant but limited increase in TBM after 28 weeks of treatment: 2.5 kg in the COBRA group, versus 0.7 kg in the SSZ monotherapy group. No data on body composition was reported. Other GC combination therapy studies only reported effects on TBM after two years of treatment, with a significant weight gain of 3 kg in the GC treatment group, and some did not report on body composition at all.

The effect of GC’s on body composition is thus often neglected, however, assessment of body composition is important in RA patients. Increased FM may cause unfavourable cosmetic effects and, since abdominal FM is an important reservoir of pro-inflammatory cytokines, it is also associated with cardiovascular morbidity and mortality. Furthermore, decreased LM may decrease functional capacity and has serious consequences for morbidity and mortality. In this study, we did not demonstrate a dose-dependent effect of COBRA versus COBRA-light treatment on body composition. Perhaps, the difference in prednisolone doses between both treatment groups, 525 mg after 26 weeks, was not large enough to cause a dose-dependent effect. Hence, we based our conclusions on the results of all patients of the primary analysis group, and not per treatment group.

Overall, there was a general worsening of BMI status in our study population: more patients became overweight and obese after 26 weeks of GC treatment. However, BMI has a very limited value for assessment of body composition in RA patients, as it does not distinguish between FM and LM, while RA patients often have an abnormal body composition. In addition, high doses prednisolone may lead to fat accumulation and fat redistribution from extremities to the trunk and abdominal area. Therefore, we focused on the specific effects on FM, and in particular on the TPFR and the proportional distribution of TBM and FM.

The TPFR remained stable after 26 weeks of GC treatment. In addition, no significant redistribution of trunk and peripheral FM was found in the log-ratio analyses. Furthermore, there was no significant change in the proportional distribution of TBM between LM, FM and BMC over time. Earlier reports about the efficacy of the COBRA-light study demonstrated a rapid decrease in DAS and inflammation parameters, which may decrease hyper-metabolism and the likelihood of cachexia. In addition, we recently reported a rapid, significant increase in physical activity in these patients, which may have
positive effects on both FM and LM.\textsuperscript{27} Thus, effective treatment with GC's counteracted the negative effects of inflammation on body composition, whereas increase in physical activity contributed to a healthier body composition, both preventing a significant change in the FM distribution.

A limitation of our study is the lack of a control group of patients who did not use prednisolone. However, a study population without prednisolone would have introduced a significant selection bias: prednisolone is not prescribed when disease is relatively mild or when patients have contra indications (e.g. diabetes mellitus or uncontrolled hypertension), indicating impaired health situation. As such, results presented in this paper cannot be solely attributed to the use of GC's.

Another potential limitation of our study might be the relative short follow up period of 26 weeks. However, all patients received the highest and largest prednisolone dose in this period, and thus the largest impact could be expected here. In addition, patients with low disease activity tapered and stopped prednisolone after 26 weeks, leading to larger differences between patients with respect to cumulative and mean prednisolone doses.

Another limitation might be the relatively small sample of patients who had a baseline DXA before start of treatment. The main results and conclusion of this study are based on the results of this smaller study population in the primary analyses, although the larger study population in the secondary analyses showed similar trends.

Furthermore, body weight, or more specifically FM and LM, were not available in the period before disease onset. Therefore, it was not possible to discriminate between increase and recovery. We hypothesized that patients with high disease activity at baseline were more likely to be ‘cachectic’, i.e. lost more weight before diagnosis than those with low disease activity, and thus would gain more weight after start of treatment. Yet, no clear association was shown between baseline DAS and change in body weight between baseline and 26 weeks (data not shown). It is therefore not very likely that the gain in bodyweight is largely attributable to recovery.

Strengths of our study include the prospective design and trial setting: all patients were GC- and DMARD-naive, had recent-onset RA, and active disease at baseline. Another major strength is the performance of log-ratio analysis, which is an advanced analysis method specifically designed for analyzing compositional data such as body composition parameters. So far, this analysis method has been used rarely, if at all, in earlier studies on body composition; neglecting the mutual, proportional relation of variables, which likely leads to overanalysis and multiplicity of statistical tests.

In sum, this study demonstrates that early RA patients treated for 26 weeks with two different high-dose, step-down GC regimens increase their TBM, because of an increase in FM. This may have some negative impact on patient health. Yet, we did not demonstrate a dose-dependent effect of the described GC treatments, nor fat redistribution, fat accumulation or muscle wasting, which would have been worse for patient health. Our results suggests that the recently reported rapid decrease in inflammation and increase in
physical activity in this study population counteracted negative side effects of short-term GC treatment on body composition in early RA patients. The absence of fat redistribution from peripheral to central tissues contradicts the widely held assumption of rapid adverse effects of prednisolone on body composition in RA.
Funding
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Disclosure statement
M.B. has acted as consultant for Pfizer and Mundipharma. All other authors have declared no conflicts of interest.
Chapter 5 Prednisolone and body composition in early RA

References


