Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis

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Background & aims: The recently proposed definitions of 'pre-cachexia' and 'cachexia' might offer new possibilities for the detection of malnutrition in patients with rheumatoid arthritis (RA).

Methods: The prevalence of different components of nutritional status and the compiled definitions of 'precachexia' and 'cachexia' were measured in a cohort of 103 patients with moderately active RA. Nutritional status was determined by measuring unintentional weight loss, BMI, and muscle strength. Bio-electrical Impedance Analysis (BIA) was used to determine fat free mass index (FFMI) and fat mass index. In addition, appetite, pain, fatigue, and inflammatory activity were assessed. The prevalence of 'pre-cachexia' and 'cachexia' was calculated from different combinations of these parameters.

Results: 20% of the study population had a low FFMI (<10th percentile), and 95% had a decreased muscle strength (<lowest tertile). Weight loss and loss of appetite, both essential elements in the newly proposed (pre-)cachexia definitions, were uncommon. The prevalence of 'pre-cachexia' and 'cachexia' was both 1% (n=1).

Conclusions: In spite of altered body composition and impaired body function, the recently proposed definitions of both 'pre-cachexia' and 'cachexia' were unable to identify and diagnose impaired nutritional status in RA patients mainly because of low prevalences of weight loss and decreased appetite.
Introduction
Both ‘cachexia’ and ‘pre-cachexia’ have recently attracted much attention in the international literature. Consensus definitions have been drafted and are now ready to be applied in different patient populations.1,2

In patients with rheumatoid arthritis (RA), an altered body composition, specifically a decreased fat free mass (FFM) in combination with a stable or increased fat mass (FM) has been described, so-called ‘rheumatoid cachexia’.3 Low physical activity, joint stiffness, pain, swelling, disuse of muscles, and metabolic changes in the body are all factors which may contribute to loss of muscle mass and strength in RA patients. The prevalence of ‘rheumatoid cachexia’ has been described to occur in up to two thirds of patients.4,5

In daily clinical practice, easy bed-side methods for the early detection of malnutrition in RA patients are lacking. If the new definitions of pre-cachexia and cachexia would be able to identify patients at increased nutrition risk, their practical application could be of additional value in the evaluation of RA patients.

Therefore, we studied the applicability of the new consensus definitions of pre-cachexia and cachexia in patients with rheumatoid arthritis.

Methods

Population
From March to June 2011 we cross-sectionally determined the nutritional status of 103 consecutive RA patients visiting the outpatient or day treatment department of Rheumatology at the VU University Medical Center, Amsterdam, the Netherlands. This study was approved by the medical ethical committee of the VU University Medical Center and all patients gave their written informed consent before inclusion.

Measurements of disease activity and nutritional status
Mean disease duration was recorded and disease activity was measured using the disease activity score based on 28 joints (DAS28)6 and Rheumatoid Arthritis Disease Activity Index (RADAI).7 Physical activity was assessed using the Health Assessment Questionnaire – Disability Index (HAQ-DI).8

Nutritional status was determined by measuring unintentional weight loss, BMI, and hand grip strength. Decreased hand grip strength was defined as handgrip strength below the third tertile of an age and sex matched reference population.9 Fat free mass index (FFMI) and fat mass index (FMI) were determined by bioelectrical impedance analysis (BIA). BIA measures were made using a QuadScan 4000 device (Bodystat Ltd, Isle of Man, UK), and the 50 kHz data were applied to a published equation generated from a cohort of healthy elderly adults: FFM (kg) = - 4.104 + (0.518 height²/resistance) + (0.231 weight) + (0.130 reactance) + (4.229 sex).10
Low FFMI was defined as FFMI below the 10th percentile, based on reference values of a large age- and sex-matched Swiss reference population. In addition, appetite (both the anorexia/cachexia section of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire and a visual analogue scale (VAS)), pain (VAS), fatigue (VAS), and inflammatory activity (Erythrocyte sedimentation rate (ESR) >10.0 mm/h, C-reactive protein (CRP) serum level >8.0 mg/L, and anemia (defined as hemoglobin (Hb) level <7.5 mmol/L for women or <8.5 mmol/L for men) were assessed.

The prevalence of ‘pre-cachexia’ was assessed following criteria as described in a recent consensus paper by Muscaritoli et al: underlying chronic disease, unintentional weight loss ≤5% of usual body weight during the last six months, chronic or recurrent systemic inflammatory response, and anorexia or anorexia-related symptoms.

The prevalence of ‘cachexia’ was based on diagnostic criteria of Evans, which include weight loss of at least 5% in twelve months or less in the presence of underlying illness and three of the following criteria: decreased muscle strength, fatigue, anorexia, low FFMI, or abnormal biochemistry.

**Results**

One hundred and three RA patients were included, median age 60 year (range 26-90 year), median disease duration 8 years. The disease activity score based on 28 joints (DAS28, mean 3.32 points) and Rheumatoid Arthritis Disease Activity Index (RADAI, mean 3.30 points) indicated moderate disease activity in this cohort. Based on the results of the Health Assessment Questionnaire – Disability Index (median 0.88 points), patients indicated mild to moderate disability.

The table (Table 1) depicts the different parameters of nutritional status in our cohort of 103 patients: 11% (n=11) of the patients experienced unintentional weight loss (≤5% bodyweight) during the past six months. Only one patient (1%) experienced ≥5% unintentional weight loss during the past twelve months. In addition, 3% of our population had a BMI <20 kg/m², 57% of our population was defined overweight (BMI >25 kg/m²), and 18% obese (BMI >30 kg/m²).

In total, 65 patients underwent BIA measurements. Of these 65 patients, 20% had a low muscle mass according to their FFMI (<10th percentile), and 31% had a high FMI (>90th percentile) which may indicate obesity. When comparing the patient subgroup with (n=65, 63%) and without (n=38, 37%) BIA measurements, age was significantly lower in the patient subgroup with BIA measurements, compared with the patient subgroup without BIA measurement (58 vs. 64 year, respectively). In addition, disease duration and number of comorbidities were significantly lower in the patient subgroup that was analyzed by BIA.

Furthermore, 95% of the total cohort had a hand grip strength below the lowest tertile, reflecting decreased muscle strength.
TABLE 1. Nutritional status parameters, determinants and prevalence of (pre-)cachexia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=103)</th>
<th>Women (n=79)</th>
<th>Men (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional weight loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5% weight loss, past 6M (n=103)</td>
<td>1 (10.7)</td>
<td>7 (8.9)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>≥5% weight loss, past 12M (n=103)</td>
<td>1 (1.0)</td>
<td>-</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Body composition parameters (BIA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFMI &lt;10th percentile (n=65)</td>
<td>13 (20.0)</td>
<td>12 (22.2)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>FMI &gt;25th percentile (n=65)</td>
<td>62 (95.4)</td>
<td>51 (94.4)</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>FMI &gt;90th percentile (n=65)</td>
<td>20 (30.8)</td>
<td>16 (29.6)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Muscle strength &lt; lowest tertile (n=103)</td>
<td>98 (95.1)</td>
<td>75 (94.9)</td>
<td>23 (95.8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS ≤50 (n=103)</td>
<td>11 (10.7)</td>
<td>9 (11.4)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>FAACT ≤24 (n=103)</td>
<td>6 (5.8)</td>
<td>5 (6.3)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Fatigue (VAS &gt;50) (n=103)</td>
<td>58 (56.3)</td>
<td>46 (58.2)</td>
<td>12 (50.0)</td>
</tr>
<tr>
<td>Abnormal biochemistry (n=100)</td>
<td>61 (59.2)</td>
<td>45 (59.2)</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>‘Pre-cachexia’ (n=103)</td>
<td>1 (1.0)</td>
<td>1 (1.3)</td>
<td>-</td>
</tr>
<tr>
<td>‘Classic cachexia’ (n=103)</td>
<td>1 (1.0)</td>
<td>-</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

BIA = Bioelectrical Impedance Analysis, FFMI = Fat-Free Mass Index, FMI = Fat Mass Index, VAS = Visual Analogue Scale, FAACT = Functional Assessment of Anorexia/Cachexia Therapy, Abnormal biochemistry = Erythrocyte Sedimentation Rate >10 mm/h, or C-Reactive Protein > 8.0 mg/L or anemia (♂: hemoglobin <7.5 mmol/L, ♀: hemoglobin <8.5 mmol/L).

Moreover, our cohort of RA patients generally exhibited relatively high appetite scores, with anorexia being present in 6% of the population when assessed with the FAACT questionnaire (cut-off value 24 points), and in 11% of the population when assessed by VAS (cut-off value 50 mm). Furthermore, fatigue was a commonly reported symptom in our cohort (56%). In addition, elevated ESR (59%), elevated CRP (24%) and anemia (14%) resulted in an ‘abnormal biochemistry’-status in 59% of the study population.

**Discussion**

Although the nutritional status of RA patients seems to be distorted in a large proportion of patients, the recently published ‘pre-cachexia’ and ‘cachexia’ definitions do not seem to offer new possibilities for the early detection of a deteriorated nutritional status in these RA patients with moderate disease activity, all treated according to standard guidelines, targeted at inducing remission.

Unintentional weight loss and loss of appetite are considered essential criteria for both ‘pre-cachexia’ and ‘cachexia’, however, these were both not very common in our study population. Often, patients with newly detected RA present themselves with loss of body weight, which increases again when the disease goes into remission. In the long term, as a result of pain and low activity levels, loss of FFM is often compensated by a gain in
FM, resulting in maintained or even increased body weight. Patients participating in this cross-sectional study had a median disease duration of 8 years. We therefore anticipated stable or even increased body weights in the majority of patients, which was confirmed by our data.

Anorexia could be a decisive component in the diagnosis of pre-cachexia in patients with RA. Disease, weight changes and inflammatory parameters belong to the routine measurements at outpatient visits. If pre-cachexia could be diagnosed easily by only adding an appetite questionnaire to the usual diagnostic palette, this could be very helpful in the early diagnosis of early malnutrition. However, only few patients reported low appetite. Increasing the FAACT cut-off point from 24 to 30, as has been suggested at ESPEN 2011, did not change our conclusions.

BIA could play an important role in the early detection of patients at increased nutritional risk, as it is described as a relatively easy bedside method used for assessment of body composition. Still, BIA may be too time-consuming for daily use during patient examinations, requiring at least ten minutes per patient. This was indeed the most important reason for not having BIA measurements in our complete cohort. In general, only patients who were treated at the day treatment unit had time enough to undergo the BIA measurements. Furthermore, to date there have been no validation studies of BIA in the RA population. We chose the Kyle single-frequency BIA equation for FFM because it was derived from elderly adults, which most closely matched our study population, and because healthy reference data could be compared to our study population.10,12 However, because the equation was generated in healthy elderly individuals, it may not be valid in our elderly RA population. Although RA patients are not known to exhibit significant deviation from normal hydration status, it is possible that the BIA-derived FFM estimates were inaccurate due to potential violation of methodological assumptions due to the RA disease activity. However, RA patients are not well-known with large deviations from normal hydration status, and therefore we suppose that the outcomes give a reliable estimate of body composition. An earlier study found a relatively good agreement at the group level between dual-energy x-ray absorptiometry (DXA, often used as the gold standard a reference method for the estimation of FFM body composition) and BIA measurements in RA patients, although the limits of agreement were wide, suggesting poor agreement at the individual level.13

Almost all patients showed a handgrip strength below the lowest tertile of the reference population. This confirms earlier reported prevalence rates of up to 80%.14 In post-hoc analyses, grip strength measurements were negatively correlated to disease duration, but not to actual disease activity. In our opinion, the outcome of handgrip strength measures are, therefore, more reflective of the consequences of the rheumatic disease than of nutritional status. In addition, the measure is too insensitive as an indicator of malnutrition, as it identifies 95% of the patients at reduced strength.
Conclusion
The recently proposed definitions of both 'pre-cachexia' and 'cachexia' are not clinically useful to identify and diagnose impaired nutritional status in RA patients treated with currently available antirheumatic drugs. They clearly underestimate the diminished nutritional status, as characterized by the individual components. We, therefore, advise to rely on individual components of nutritional status when performing nutritional assessment in RA patients.
Chapter 6

**Conflict of interest**
We received no funding for this study.

**Statement of authorship**
MvB, NK and LvT designed the study; all authors approved the study protocol. NK collected the data. MvB, NK and LvT conducted the data analyses. MvB and NK drafted the manuscript. All authors provided advise on the writing of the manuscript and approved the final version of the manuscript.
References