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Review

# Cachexia and adiposity in rheumatoid arthritis. Relevance for disease management and clinical outcomes

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ABSTRACT

Altered body composition is a frequent finding in rheumatoid arthritis and is associated with the two major outcomes of the disease: disability and cardiovascular mortality. It is estimated that up to two thirds of patients may be affected by loss of lean mass, the so-called rheumatoid cachexia. Hence, body weight being equal, the relative amount of lean mass is lower and that of body fat is higher in rheumatoid arthritis patients vs. healthy controls. Both disease-related factors and other factors, like drug treatments, physical activity and nutrition contribute to modify body composition in rheumatoid arthritis. The effect of pharmacological treatments, and notably of anti-TNF drugs, on body composition is controversial. Conversely, training programs to stimulate muscle growth can restore lean mass and reduce adiposity. There is good evidence that amelioration of body composition ameliorates function and reduces disability. Currently, there is no evidence that interventions that modify body composition can reduce cardiovascular morbidity and mortality in rheumatoid arthritis.

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## 1. Introduction

Body composition (BC) is a term that refers to the relative amounts of the different compartments of the body, notably fat mass (FM) and fat-free mass (FFM), the latter comprising body water, bone and body cell mass (BCM). BC is a reflex of the reciprocal interaction of genetic and environmental factors, like nutrition and physical activity. For this reason, BC displays a high variability in the general population. Moreover, BC varies in different pathological states, and there is evidence that chronic autoimmune and inflammatory conditions, like rheumatoid arthritis (RA), can profoundly modify BC. RA causes increased disability and cardiovascular (CV) mortality [1,2]. Interestingly, both these outcomes are associated with an altered BC in the general population. Hence, the study of BC in RA is particularly intriguing, and may allow to better understand the major complications of the disease. As an altered BC reflects chronic metabolic perturbations induced by RA, the study of BC might help in detecting patients with worse prognosis. More interestingly, during the course of the disease, the altered BC may become an active participant in inducing disability and mortality, which suggests that treatments targeting BC might contribute to lower the disease burden of RA.

## 2. Is there a healthy body composition?

In clinical and epidemiological practice, normal weight, overweight and obesity are categorized on the basis of the body mass index (BMI) (i.e. body weight divided by height squared). Epidemiological studies suggest the lowest morbidity and mortality rates in subject with BMI comprised between 19 and 25 [3]. Nevertheless, BMI is not a biological trait but a calculated value that poorly reflects the nutritional and metabolic state. There is evidence that normal weight subjects, with low subcutaneous but increased visceral fat mass are insulin-resistant and have increased cardiometabolic risks. Moreover, about 30% of obese subjects have a favorable metabolic profile, i.e. absence of metabolic complications, inflammation, dyslipidaemia and hypertension [4]. Compared with obese patients with high cardiometabolic risks, these subjects have lower fat infiltration in the liver and in skeletal muscle. This underlines the need to better describing multifaceted phenotypes to provide useful information about physiological and pathological states. BC is a better proxy of physiological and pathological states [5]. There is an association between BC, morbidity and mortality, in

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particular both low lean mass (LM) and high fat mass (FM) are associated with higher burden of disease morbidity and longer hospital stay [6]. Even the assessment of BC shows limits at predicting morbidity. For example, visceral fat (VF) is more predictive of insulin resistance than subcutaneous fat, and fat liver infiltration is more related to insulin resistance than whole VF; moreover, around 40% of people with fatty liver are not insulin-resistant [7]. Despite these limitations, "healthy" body fat (BF) percentages based on the lowest cardiovascular mortality in general population are set between 12 and 20% for men and between 20 and 30% for women. Overweight is defined by BF percentage > 25% for men and > 33% for women. Obesity corresponds to BF percentages > 29% for men and > 41% for women. To take into account the relative loss of muscle mass that intervenes with aging (sarcopenia, see after), people over 60 years are considered obese at BF percentages > 31% and > 43% in men and women, respectively [3].

Differently from BF, desirable percentages of LM are less well-defined in general population. Apart from aging, loss of LM is almost always associated with disease states. Sarcopenia in healthy aging people results in light reduction of BCM, which suggest that conservation of BCM is critical for health and survival. Studies on extremely undernourished people, in AIDS and in cancer, have shown that erosion of BCM to around 60% is invariably linked to death [8]. As a rule of thumb, one may retain that a healthy BC consists of conservation of BCM to the higher extent and limitation of BF percentage within the limits mentioned before.

## 3. Measures of body composition

### 3.1. Definitions

In order to avoid ambiguity about conditions of altered body composition, a standardized nomenclature has been proposed [8] (Text S1; See the supplementary material associated with this article online). Sarcopenia indicates the specifically involuntary loss of muscle mass, which typically accompanies aging. Wasting refers to involuntary weight loss with loss of both LM and FM; cachexia refers to involuntary exquisite loss of BCM or LM with little or no global weight loss (i.e. muscle is replaced by fat). This means that everybody who has wasting has cachexia, while the opposite is not true. Importantly, cachexia and wasting depend on different pathophysiological processes. Cachexia is the result of the inflammatory response that increases the resting energy expenditure (REE) and dissipates LM despite adequate dietary intake. Wasting intervenes when dietary intake is poor. Patients with cancer are cachectic in the first phases of the disease, when dietary intake is normal, and become wasted later when anorexia appears.

### 3.2. Body composition and disease in the general population

#### 3.2.1. Body composition in rheumatoid arthritis

Rheumatoid arthritis is characterized by increased CV mortality, with a mean reduction of life expectancy of 5–10 years [9,10] (Text S1; See the supplementary material associated with this article online). Disability is another cardinal feature of the disease, resulting in high direct and indirect costs for the community. Since both these outcomes may be associated to an altered BC in RA patients, it seems crucial to determine:

- the frequency of altered BC in RA;
- which factors contribute to alter BC;
- whether these factors are modifiable;
- whether modifications of these factors modifies BC and, ultimately, disease outcomes.

It is estimated that up to two thirds of RA patients are affected by loss of BCM, the so-called rheumatoid cachexia. This entity, clinically recognized by Paget in 1873, and attributed to the neurological involvement of the disease, has been neglected for a long time. In the early 1990s, Roubenoff et al. recognizing the frequency of this condition, coined the term "rheumatoid cachexia" and first postulated a link between the inflammatory process of RA and changes in BC [11].

Activation of the immune system is a highly energy-consuming process [12], inducing a hypermetabolic, catabolic state with increased REE [11] that seems directly correlated to cytokine production. The consequence is chronic erosion of BCM resulting in a cachectic state. Rheumatoid cachexia is associated with low bioavailability of insulin-like growth factor [13] but, differently from sarcopenia of aging, does not depend on reduced testosterone or growth hormone production [14].

For most cachectic RA patients, especially if dietary intake is normal, total body weight is not reduced and the loss of muscle is partially compensated by an increase in BF. Hence, body weight being equal, the relative amount of LM is lower and that of BF is higher in RA patients vs. healthy controls. This renders BMI a particularly inadequate proxy of BC in RA. To take into account this increased adiposity, it has been proposed that BMI thresholds for overweight and obesity in RA should be reduced respectively to 23 and 28 [15]. BMI is also an inadequate detector of LM loss: in a case-control study, BMI was unable to detect rheumatoid cachexia as assessed by DXA in 26% of women and 21% of men [16]. In a cohort of patients with moderately active disease, 44% of women with a normal BMI had low fat-free mass index (FFMI), while 40% of women and 75% of men in the normal BMI category had high or very high fat mass index (FMI) [17]. Despite these limitations, BMI is related to several outcomes in RA, and patients with BMI < 18.5 show the highest CV risk [18] and highest rates of erosive disease [19]. Patients with lowest BMI are not only affected by most severe cachexia (Fig. 1), but are also likely to have low adiposity, that is, they are wasted.

This evokes the complexity of pathophysiology of altered BC in RA. Apart from inflammation, BC is the result of a complex network of interconnected factors, like physical activity, nutritional intake, chronic corticosteroid treatment and may participate in a vicious circle that results in poor disease outcomes (Fig. 2). The contribution of each factor can be extremely variable, and difficult to dissect, especially if one considers that most studies on BC have a cross-sectional or a case-control design. Despite this complexity, it is assumed that altered BC starts with the inflammatory process of RA. This is supported by the results of studies in early disease. In a Swedish cohort of early RA (mean disease duration 7 months), both men and women had significantly lower LM of arms and legs compared to healthy controls [20]. Women had even higher total and truncal fat (26.1 vs. 23 kg and 12.1 vs. 11.3, respectively). In a cohort of 105 Vietnamese women with RA of less than 3 years of duration, body weight and BMI did not differ from age-matched controls while appendicular LM was lower and FM and total and truncal FM significantly higher [21].

Moreover, several other studies after those of Roubenoff et al., found a direct association between cytokine production and rheumatoid cachexia. In a transversal study on 97 RA patients, around 50% of patients felled into the lowest 10th centile of a reference control population for upper arm muscular area. The loss of total LM was correlated to acute phase response [22]. In a case-control study, 20 women with early RA had 14% lower BCM than controls. The loss of BCM was correlated to TNF-alpha production from their peripheral blood mononuclear cells. No correlation with IL-1 or IL-6 production was found [23]. This kind of association was detected even in long standing RA. In a Swedish case-control study, 50% of patients with 13-year mean RA duration had rheumatoid

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