

# *Sarcopenia in rheumatoid cachexia: definition, mechanisms, clinical consequences and potential therapies*

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## RESUMO

Rheumatoid cachexia can be defined as an involuntary loss of body cell mass, which predominates in skeletal muscle, but is also observed in the viscera and immune system. It occurs with little or no weight loss in the presence of stable or increased fat mass. The etiology is likely multifactorial, and involves excessive inflammatory cytokine production, namely excess tumor necrosis factor- $\alpha$  and interleukin- $1\beta$  production, reduced peripheral insulin action, and low habitual physical activity. Cachexia occurs in active rheumatoid arthritis and even in the presence of disease control. In this article, we discuss the pathogenesis of rheumatoid cachexia, its clinical implications and potential therapies.

**Keywords:** body composition, cachexia, rheumatoid arthritis, sarcopenia.

## INTRODUCTION

Skeletal muscle forms the largest body tissue, comprising the largest cell mass and protein component in the organism.<sup>1</sup> The muscular tissue, responsible for motion autonomy, takes part not only in metabolic and glycemic homeostasis, supplying amino acids to other tissues, but also in fat oxidation, oxygen fixation and energy expense modulation at rest.<sup>1</sup>

Muscle mass results from the balance between synthesis (anabolism) and catabolism (destruction) of its proteins, especially myofibrillar proteins. Catabolic factors include insulin resistance and high glucocorticoid levels, denervation, inflammatory stress, disuse, calorie restriction, acidosis and oxidative stress. Additionally to endangering strength, power and balance, muscle hypotrophy is associated with insulin resistance, Diabetes mellitus type II, hyperadiposity, lower tissue repair, and immunity incompetence.<sup>1</sup>

## SARCOPENIA

Muscle mass loss associated with function damages form a syndrome entity named sarcopenia. The most common is senile sarcopenia;<sup>3,4,5</sup> however, poor energy, HIV and chronic inflammatory diseases (for example, RA) may result in sarcopenia in non-elderly subjects.<sup>4,5,6,7</sup>

Baumgartner<sup>8</sup> defined sarcopenia as a reduction of skeletal muscle mass of standard deviation below the mean of the control group, formed by healthy young subjects (29 years old), paired with the same race. Based on these criteria, 13-24% prevalence was found in the age group ranging from 65 to 70 years old and more than 50% in subjects over 80 years old. Sarcopenia arises from the interaction of enervation disorders (reduction of motor neurons accelerated by high number of drugs generally taken by elder people), reduction of physical activity, reduction of hormones, increasing inflammatory

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mediators and changes of protein and calorie ingestion that happen during aging.<sup>9,10,11,12</sup>

It is important to say that sarcopenia is different from cachexia caused by inflammatory diseases, advanced chronic diseases, debilitating muscle disease or malnutrition.<sup>12,13,14</sup> In those situations, if a reduction of skeletal muscle mass (sarcopenia) happens, it is only one of the manifestations of a more complex syndrome named cachexia, which is the sarcopenic component of cachexia. Cachexia is characterized by anorexia, weight loss, hypoalbuminaemia, anemia, changes in the wound healing process and in immunocompetence.<sup>2</sup>

## CACHEXIA

In Greek, it means poor condition. That word was commonly related to patients in bad general state, with consumptive diseases, high malnutrition level and weakening. Today, cachexia refers to the loss of body cell mass due to diseases,<sup>16</sup> followed by muscular mass loss (sarcopenic component); it should be understood as a multidimensional adaptation approaching a wide variety of changes, from physiological changes to behavior changes.<sup>15</sup> Frequently, patients with chronic or terminal diseases, such as cancer, AIDS, congestive heart failure, tuberculosis, chronic obstructive pulmonary disease, cystic fibrosis, rheumatoid arthritis (RA), Crohn's disease, and others, present cachexia.<sup>15</sup> Table 1 shows the main metabolic changes found in cachexias.

Cachexia associated with RA was first described in 1873 by Sir James Paget;<sup>17</sup> this term refers to body cell mass loss and high energy consumption at rest, which occurs in RA and is not necessarily related to weight loss, since in several patients loss of body cell mass is followed by increasing fat mass, but weight is still stable.<sup>13,16,19-21</sup> Those cases are referred to as obese cachexia.<sup>13,22</sup> Loss of body cell mass is more marked in skeletal muscles (sarcopenic component) but also observed in viscera and immune system. Its consequences<sup>22</sup> are listed in Figure 1.

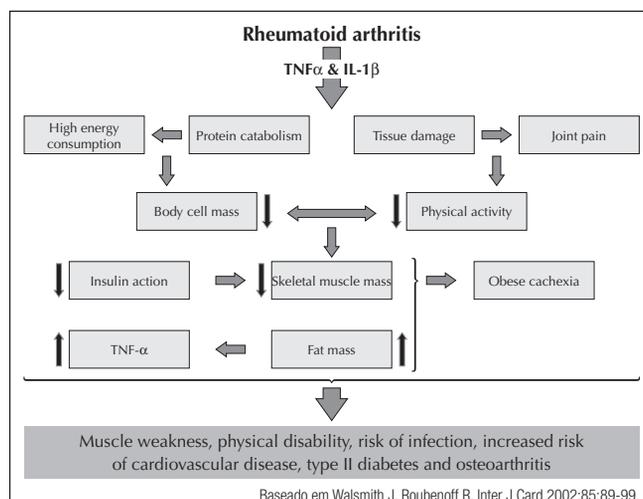
**Diagnosis and classification of the sarcopenic component of rheumatoid cachexia:** The presence of cachexia and its sarcopenic components in the RA patient<sup>23</sup> depends on the body composition evaluation, which may be performed by several methods, like nuclear magnetic resonance, CAT scan, bioimpedance, ultrasound, DEXA bone densitometry and anthropometric measures. For example, body cell mass may be measured by calculating the total body potassium;<sup>16,24</sup> its reduction is one of the cachexia indices. At this moment, the most used method is densitometry, which makes it possible to evaluate body composition, bone mass, body cell mass and

total fat mass.<sup>9</sup> If DXA is not available, body composition may be evaluated by using anthropometric measures; it requires scales, measuring tape and body caliper (Lange®). Applying these simple instruments, body fat may be indirectly measured using the waistline-hip ratio (RCQ) proposed by Ashwell.<sup>25</sup>

**Table 1**  
Metabolic changes found in cachexias

I. Protein
Elevated urinary nitrogen
Elevated protein turnover
Reduction of muscular protein synthesis
Catabolism of increased skeletal muscles
Increasing proteins in acute phase
II. Lipids
Increased lipolysis
Reduction of lipogenesis
Hyperlipemias
Increasing turnover of free fatty acids
Reduced activity of serum lipoprotein lipase
Increasing synthesis of new fatty acids
III. Carbohydrates
Glucose intolerance
Hyperinsulinemia
Insulin resistance
Increasing glucose turnover
Increasing neoglucogenesis

Changed from Kotier PD. Ann Intern Méd 2000; 133:622-34.



**Figure 1.** Summary of metabolic consequences of rheumatoid arthritis.

Circumference measures of the arm (CB), forearm (CAT), chest (CA), hip (CQ), thigh (CC) and calf (CP) make it possible to calculate muscle mass (MM) and muscle mass index (IMM), allowing sarcopenia diagnosis and classification.

Calculation of muscle mass (MM kg) is obtained by the Lee equation.<sup>26</sup>

$$MM \text{ (kg)} = \text{height}^2 \times (0.00744 \times \text{arm circ.}^2 + 0.00088 \times \text{thigh circ.}^2 + 0.00441 \times \text{calf circ.}^2) + 2.4 \times \text{gender} - 0.048 \times \text{age} + \text{race} + 7.8$$

Gender = man 1; woman 0

Race = -2.0 Asian; 1.1 Black; 0 White

Muscular mass index (MMI) is obtained by a simple calculation: MM (kg)/height (m)<sup>2</sup>.

It is necessary to say that, in rheumatoid arthritis, reduction of muscular mass index occurs due to an inflammatory process, forming the sarcopenia component of rheumatoid cachexia. That is the component we can diagnose and classify by using anthropometric measures.

Sarcopenia classification is obtained with muscular mass index (MMI). According to the classification proposed by Jansen,<sup>27-29</sup> for men, a normal MMI is 10.75 kg/m<sup>2</sup>, sarcopenia grade I – 10.75 > MMI ≥ 8.51 kg/m<sup>2</sup>, and sarcopenia grade II – MMI < 8.51 kg/m<sup>2</sup>; for women, a normal MMI is ≥ 6.75 kg/m<sup>2</sup>, sarcopenia grade I – 6.75 > MMI ≥ 5.76 kg/m<sup>2</sup>, and sarcopenia grade II – MMI < 5.76 kg/m<sup>2</sup>.

**Physiopathologic mechanisms that cause rheumatoid cachexia:** Several factors contribute to the rheumatoid cachexia development and its sarcopenia component; therefore, we can assure that its etiology is multifactor and includes insufficient physical activity, excessive inflammatory cytokines, hormone changes, improper body energetic profile, and protein turnover dysfunction.<sup>13,16,22,24</sup> In RA, chronic inflammation is responsible for protein and metabolism change; it also accelerates the synthesis-degradation ratio,<sup>22</sup> which facilitates loss muscle and bone mass. The most common muscle active cytokines (myocytokines) are: tumoral necrosis factor-alpha (TNF $\alpha$  or cachexin), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6), interferon gamma (INF- $\gamma$ ), and growth factor beta (TGF- $\beta$ ). These cytokines, which have an important role in RA pathogenesis,<sup>16</sup> take part not only in joint damaging, but also interfere in the total body protein and energy metabolism. TNF $\alpha$  is probably the main mediator of muscle dysfunction; it contributes to cachexia accelerating muscle catabolism and causes loss of muscle mass (sarcopenia component). TNF $\alpha$  works synergically with IL-1 $\beta$ , another proinflammatory cytokine that also contributes to cachexia installation.<sup>22</sup> Another TNF $\alpha$  effect is mediating insulin resistance and indirectly promoting cachexia by reducing peripheral insulin action and

relieving its anticatabolic effect.<sup>22</sup> The loss of muscle protein also depends on INF- $\gamma$  signaling and transcription of nuclear factor kappa B (NF-kB).<sup>13</sup>

Reduction of food consumption may be another factor that contributes to develop cachexia. The inverse association between IL-1 $\beta$  production and diet ingestion suggests that this cytokine production leads to relative anorexia, which may aggravate the loss of body cell mass that is characteristic to this hypercatabolic state of a chronic inflammatory disease. Increasing ingesta, facing high energy needs, is a healthy attempt to improve energetic balance.<sup>16</sup>

Analyzing this energetic balance in a chronic inflammatory disease, it is necessary to consider total daily energetic expense. Studies suggest that energy expense at rest is higher in rheumatoid; on the other hand, energy expended with exercises is lower. TEE – *total daily energy expenditure* is the sum of *resting energy expenditure* – REE plus the EEPA – *expenditure of physical activity* and the TEF – *thermic effect of food*, according to the following formula:<sup>13</sup> TEE = REE + EEPA + TEF.

Although REE is high in RA,<sup>16,30</sup> TEE also depends on EEPA.<sup>13</sup> Low physical activity is responsible for 77% of the difference in TEE between rheumatoid people and healthy people, which shows that low physical activity is an important determinant factor of low TEE in RA, causing a predisposition to gain fat mass.<sup>20</sup>

Although a good control of rheumatoid diseases activity not always prevent the development of cachexia<sup>20</sup> and associated sarcopenia, it certainly contributes to hypermetabolism (high REE) to be less stressed.<sup>11</sup>

**Clinical consequences of rheumatoid cachexia:** Some general (non-articular) manifestations, such as fatigue feeling, illness, indisposition, anorexia, and sleep changes, occur both in rheumatoid patients and patients with rheumatoid cachexia and should be related to pro-inflammatory cytokine<sup>15</sup> (Table 2). Also with extra-articular manifestations, it is necessary to consider that muscles form the main deposit of body proteins, so depletion of this protein deposit (muscle atrophy) **as part of the RA clinical condition contributes to the development of the sarcopenia component of rheumatoid cachexia** and intervenes in the patient capacity to block installation of diseases such as ischemic cardiopathy, neoplasia or even infections; its clinical consequence is higher morbidity and mortality.<sup>21</sup> Additionally to endangerment of locomotor system, the body as a whole is attacked by chronic inflammation and two thirds of rheumatoid patients develop cachexia.<sup>13</sup>

RA cachexia is different from the one observed in AIDS and neoplasias also according to prognosis. In those diseases,

**Table 2**  
Changes found in RA related to inflammatory cytokines

<b>I. Behavior</b>
Anorexia
Fatigue
Malaise
Sleep disorder
<b>II. Physiology</b>
Increasing blood temperature
Higher energy expense at rest
Reduction of muscular mass
Bone marrow suppression
<b>III. Nutrition</b>
Weight loss
Gain of fat mass
Increasing acute-phase proteins
Negative nitrogen balance
Hypoalbuminaemia
Hyperinsulinemia
Hypertriglyceridemia

Modified from Kotier PD. *Ann Intern Méd* 2000;133:622-34.

cachexia is a predictor of death, while in RA it is not directly fatal; it is related to disease activity and is considered an important factor of comorbidity, reducing life expectancy.<sup>22</sup> Body cell mass is inversely associated with the number of joint edemas, so the level of cachexia is related with synovitis intensity, that is, the more synovitis, the more cachexia.<sup>30</sup> Cachexia increases inactivity, reducing even more muscle strength, which decreases functional status and establishes a vicious circle. That is associated with loss of physical independence, and facilitates depression, reducing life quality. As loss of cell mass occurs also in viscera and in the immune system, morbidity and mortality<sup>22</sup> acceleration is observed as a consequence. It is important to say that loss of 40% of the body cell mass is lethal, despite other risk factors.<sup>16,31</sup>

Such considerations become particularly important when evaluating mortality in RA population. The life expectation of a patient with rheumatoid arthritis is reduced in two to five times when compared with general population.<sup>16,32,37,38</sup> It is known that, after 20 years with a disease, 80% of the patients presented some level of incapacity.<sup>32</sup> Death due to infection in these patients is 20 times higher than in general population, and cancer and cardiovascular diseases are also more frequent.<sup>34</sup>

In fact, an epidemiologic study showed higher cardiovascular risk in patients with RA when compared with non-rheumatoid controls,<sup>35</sup> and patients with low body mass index (BMI) ( $< 20 \text{ kg/m}^2$ ) have three times more risk of cardiovascular death than non-rheumatoid subjects with normal BMI, after correction for age, dyslipidemia, blood hypertension and smoking.<sup>21</sup> Cachexia occurs with low BMI and possibly contributes to this higher cardiovascular risk. It is important to say that non-rheumatoid populations with normal and low BMI do not present difference in cardiovascular death risk, and by that we conclude that BMI is an important predictor of cardiovascular death only in RA patients.<sup>21</sup>

Another important factor to be considered in the analysis of morbidity/mortality in RA and its relation with the presence of cachexia is hyperlipemia. In RA patients, reduction of peripheral insulin action and of physical activity has been reported, predisposing the gain of fat mass and hyperlipemia.<sup>22</sup> These metabolic changes contribute to the development of diabetes mellitus type II, osteoarthritis and cardiovascular disease.<sup>22</sup> On the other hand, loss of muscle mass, felt as a weakness sensation, contributes to inactivity and increases both cardiovascular risk and infections.<sup>16,22,36</sup> Metabolic changes that occur in rheumatoid cachexia may contribute to an increasing cardiovascular risk – they include hypertriglyceridemia (synthesis of new triglycerides), reduction of the action of lipoprotein lipase, increasing hepatic secretion of VLDL and also free fat pool.<sup>15</sup>

Cachexia metabolic changes observed in rheumatoid arthritis are considered more stressed during the disease activity. However, even when the disease is under control and metabolic abnormalities are minimized, its consequences, such as reduction of body cell mass, gain of fat mass and even functional sequelae like reduction of physical activity are not corrected without direct and specific intervention.<sup>13</sup>

**Treatment of rheumatoid cachexia and its sarcopenia component:** Treating rheumatoid cachexia implies treating its arthritis. Concerning cachexia, there is still no standard treatment<sup>22</sup>. Table 3 lists therapy measures proposed for cachexias. It is necessary to focus first on treating rheumatoid activity. Without any doubt, the use of antirheumatic drugs that modify the disease course (DMCDs) provides clinical improvement and delays the radiological development of rheumatoid arthritis,<sup>39-42</sup> however, its efficiency for cachexia and its consequences are not so evident.

Similarly, the use of non-steroidal anti-inflammatory drugs (AINEs) and corticoids (CD) focuses on aborting or minimizing inflammation. CEs used in high doses of prednisolone (1000 mg/day) during three days (pulse) are efficient to suppress

**Table 3**  
Therapy measures for cachexias

<b>Physical exercises</b>
Workout with progressive weights
<b>Hypercaloric diet</b>
<b>Appetite Stimulants</b>
Megestrol acetate
Medroxyprogesterona
Dronabinol
<b>Anabolic agents</b>
growth hormone
Sexual steroids
<b>Anti-inflammatory drugs</b>
Corticoids
Indometacin
<b>Cytokine inhibition</b>
Thalidomide
Antioxidants
Melatonin
L- Carnitine
ω3 fatty acids

Modified from Kotier PD. *Ann Intern Méd* 2000; 133:622-34.

the disease activity for four to six weeks;<sup>43</sup> however, despite the anti-inflammatory effect and appetite stimulus produced, improving food ingesta, such actions are not sufficient to minimize the catabolic effects of corticoids, worsening cachexia.<sup>31</sup> Nevertheless, low doses of prednisone (2.5 to 7.5 mg/day) may protect against loss of body cell mass as they improve the patient functional state and reduce rheumatoid inflammation, which is a catabolism mediator.<sup>16,20,24,31</sup> It is known that indometacine and prednisone association improves the survival of patients with cachexia due to cancer.<sup>45</sup>

Despite the aggressive treatment of inflammation, with CE and AINEs and the use of DMCDs such as methotrexate, this is not sufficient to recover rheumatoid cachexia, as hypermetabolism may be persistent even in patients with good clinical control of the disease activity.<sup>16,18,55</sup> Thus, after controlling the disease activity and knowing the cachexia pathophysiology, it is necessary to adopt interventions focusing on the persistent catabolism reversion, which may be classified according to the following: intervention with exercises, diet intervention and drug intervention.<sup>13</sup>

**EXERCISES:** Current knowledges point physical exercises as the most efficient intervention for sarcopenia and rheumatoid cachexia treatment.<sup>48,49,50,51,52,53,54</sup> Combining aerobic exercises and progressive weight workout are generally considered the

best intervention to combat cachexia, reduction of aerobic capacity, muscle strength, and resistance strength caused by rheumatoid arthritis. Physical activity may reduce fatigue feeling, joint edema, morning rigidity, as well as improve physical and cardiovascular performance.<sup>22,53</sup> These changes can be seen after 12 weeks of high intensity resistance treatment in patients with well controlled RA.<sup>52</sup> It suggests that such physical activities, considering the presence of inflammatory manifestations, can normalize protein metabolism in rheumatoid arthritis. It is important to say that, for a successful resistance workout in improving muscle mass, a suitable nutrition is required, as aerobic workout increases protein needs.<sup>18</sup>

**DIET INTERVENTION:** Discussions on nutritional interventions in rheumatoid arthritis always approach the influence of certain diet elements in arthritis as a whole and not specifically in cachexia.<sup>56,57,58,59</sup> Supplementation with monounsaturated and polyunsaturated fatty acids may be useful to reduce pain, the number of joint edemas and to facilitate reducing the NSAID dose. Antioxidant supplementation, like alpha tocopherol (vitamin E), should provide an important defense against the increasing oxidative stress. Low doses of folic acid, calcium and vitamin D and iron replacement are only recommended in specific situations, such as patients using methotrexate,<sup>61</sup> corticosteroid or when anemia or osteoporosis diagnosis has been clinically established.

Focusing only on metabolic changes of cachexia, it is possible to pay special attention to the nutritional status of the patient, prescribing a hypercaloric diet and reinforcing the physical activity. Although some studies clearly document hypercaloric diet benefits, there are patients with such accelerated protein degradation that cachexia superposes the possible gain induced by nutrition. It is possible to say that few published studies evaluate nutritional therapies, which makes it impossible to analyze and measure its clinical benefits.<sup>13</sup> Additionally, some authors say that protein and calories ingestion in RA patients is typically suitable; they do not believe that improper food consumption may have a significant participation in the rheumatoid cachexia development.<sup>11</sup> So we think it is logical to propose that healthy recommendations for general population, like varied and balanced diet, with food rich in antioxidants, suitable protein and calories ingestion, sufficient amounts of calcium, iron, vitamins, including vitamin D, and linolenic polyunsaturated (ω3), should be recommended to RA cachexia patients. There are no data recommending some type of diet with special requests.

**DRUG INTERVENTION:** Some drugs may be used to fight cachexia: appetite stimulant, anabolic agents and new DMCDs.

**Appetite stimulants.** Trials with HIV and cancer patients showed that stimulating appetite with megestrol acetate improves food ingestion and weight gain.<sup>15</sup> Considering that in rheumatoid cachexia the catabolism is increasing, anabolic drugs, like estrogen, testosterone, nandrolone, dehydroepiandrosterone (DHEA), and growth hormone (GH), can contribute to revert cachexia. Estrogen replacement in women has not been effective in increasing muscle mass.<sup>9</sup> On the other hand, testosterone replacement in hypogonadic men increases muscle mass.<sup>4,62</sup> After six months of replacement therapy in young men, it was possible to increase 15% of body cell mass of subjects and reduce 11% of fat mass, while muscle protein synthesis increased 56%; however, side effects require special attention. These side effects include increasing hematocrit, prostate enlargement, increased levels of prostate-specific antigen (PSA) and worsened lipid profile.<sup>4</sup> Studies with nandrolone decanoate also show muscle mass gain, but more long term studies are required to evaluate actual benefits *versus* risks.

Long term studies (9 months) showed that the use of (DHEA) did not show any benefit in muscle mass gain or fat mass loss.<sup>4</sup> GH replacement in the elderly does not increase muscle strength nor empowers gains with resistance workout, nor improves muscle protein synthesis.<sup>4,9</sup> Main adverse effects are: edema, carpal tunnel syndrome, arthralgia and gynecomastia. It is important to say that even persistent GH reduction is not associated with rheumatoid cachexia.<sup>24</sup> Considering also that recombining GH treatment is very expensive, approximately US\$1,268.00/month, we do not recommend it for cachexia treatment.

**New DMCDs.** Therapeutic response to new DMCDs (like TNF $\alpha$  blockers), widened the horizons in rheumatoid arthritis treatment, increasing the chances of a successfully therapy. However, even the use of new drugs may not be sufficient to recover rheumatoid cachexia.<sup>13,15,22,44-46</sup> We can speculate that TNF $\alpha$  blockers may keep body cell mass in rheumatoid arthritis,<sup>13</sup> although a recent study with etanercept during six months in initial RA has shown results not superior to methotrexate.<sup>64</sup> It is possible that specific blocking of the main cachexia mediator cytokine for long time may cause body cell mass normalization.<sup>66</sup> There are not too many studies, as we know, until today, analyzing the effect of those agents in the RA body composition and further studies are required to evaluate the actual efficiency and appropriate dose for specific cachexia treatment. In Table IV, possible pharmacological treatments for cachexias are shown.

## CONCLUSION

Cachexia occurs in approximately 66% of the rheumatoid arthritis patients and there is still no well established therapeutic proposal for this specific aspect of RA. However, we know that current DMCDs control rheumatoid activity and prevent radiological development but they are not sufficient to recover rheumatoid cachexia. Therapy modalities like hormone replacement, such as testosterone, DHEA and GH are either uncertain in results or prohibited due to side effects. However, it is possible that a suitable diet intervention associated with correct physical exercises intervene successfully in rheumatoid cachexia.

New DMCDs changed the development of rheumatoid arthritis, controlling the disease activity and progression of joint damage; however, further studies are necessary to assure its capacity to recover cachexia.

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