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Sarcopenia, a hidden comorbidity of established rheumatoid arthritis

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Abstract

This editorial, "Sarcopenia: a hidden comorbidity of established rheumatoid arthritis" emphasizes the critical role of addressing comorbidities in rheumatoid arthritis (RA) management, focusing particularly on the clinical impact of sarcopenia. The first section highlights how advances in treating immune-mediated rheumatic diseases have improved RA management but also underscore the increasing necessity to integrate comorbidity management to enhance patient outcomes. The second part focused into sarcopenia as a significant yet overlooked comorbidity in RA, discussing its prevalence, impact on life quality, and the complexities of its diagnosis and management. The editorial advocates for a multidisciplinary approach involving rheumatologists, nurses, and primary care physicians to effectively tackle this issue. A call to action from scientific societies is suggested to raise awareness among healthcare professionals about sarcopenia, aiming to improve care for RA patients.

Keywords

Sarcopenia, rheumatoid arthritis, comorbidity, multidisciplinary management, clinical impact, treatment

In the last two decades, there has been a revolution in the treatment of immune-mediated rheumatic diseases (IMRD). The possibility of interfering with the signals that produce and amplify inflammatory phenomena makes it possible to significantly attenuate clinical manifestations and even achieve remission of the disease, an outcome that was inconceivable a few years ago [1].

Rheumatoid arthritis [2] (RA) constitutes the paradigm of IMRD. It manifests as a complex condition with persistent and progressive joint and systemic symptoms, significantly elevating the risk of disability and mortality. It spans a broad spectrum of manifestations that amplify its overall impact, highlighting the essential need for continuous, integral strategies in management.

In parallel with pharmacological development, the care model for patients with RA has changed substantially [1, 2]. Now, it is unreservedly assumed that the response to the treatment must necessarily be

measured. Thus, the so-called "outcome measures" have emerged, a set of variables that reflect the underlying situation and allow the results of the prescribed treatment to be objectively assessed.

By having outcome measures, it is possible to predefine an objective. At each consultation, the clinician evaluates the patient's condition and, if the pre-established objective has not been achieved, systematically makes adjustments or changes in the treatment. This therapeutic strategy, called "treat to target", implies the need to frequently contact the patient to evaluate the results obtained ("tight control") [3].

Beyond the "treat to target" and "tight control", care model for RA should also include attention to patient comorbidities [4]. The comorbid processes associated with RA largely determine the prognosis of the disease. Thus, recently, Bertsias et al. [5] have demonstrated that in patients with difficult to treat RA ("D2T"), patterns of comorbidities differentially affect long-term functional evolution and disease activity and Kimbrough et al. [6] have showed that a great number of comorbidities are significantly associated with a risk of developing serious infections, a leading cause for increased mortality in RA.

Interestingly, at the onset of the disease, nearly half of the patients presented with at least one clinically significant comorbidity. Stouten et al. [7] demonstrated that the presence of comorbidities was linked to poorer functional outcomes and more severe disease activity over a two-year period, even with aggressive remission induction therapy.

The level of awareness that rheumatologists have about your responsibility in controlling RA comorbidities is not always as high as would be desirable. That said, it is clear that the idea that comorbidities are part of established RA [8] is becoming more entrenched, and that the periodic assessment of the most relevant of them, cardiovascular diseases, osteoporosis, depression, infections and neoplasms, is one of the tasks involved in treating patients with this disease.

The spectrum of processes associated with RA is increasingly broader and there is a need to analyze, in addition to these traditional comorbidities, other disorders [9] that accompany the disease and that significantly alter the patient's health-related quality of life. These "new comorbidities" includes, among others, sleep disorders, sexual dysfunction, fatigue and, especially in elderly patients with established disease, sarcopenia.

Sarcopenia is a generalized musculoskeletal disorder characterized by loss of muscle mass and function together with decreased physical performance [10]. These deficiencies lead to a higher risk of falls and hospitalization rates, decreases the ability to perform activities of daily living, worsens quality of life, and increases morbidity and mortality [11]**.** Sarcopenia is highly prevalent in older patients and is an important factor contributing to frailty and disability, generating a significant social and economic burden [12].

The data on the magnitude of sarcopenia in the community are highly variable. The prevalence [13] ranges between 12.9% and 40.4%, depending on the demographics of the study population and the diagnostic criteria applied.

Classically, a differentiation has been established between primary and secondary sarcopenia. Sarcopenia is considered "primary" if the age is the only causal factor and "secondary" when there are other determining conditions such as diseases or treatments. Although it is a somewhat anachronistic concept, it serves to show that, sometimes, sarcopenia can appear as a process associated with a specific underlying disease. Thus, it has been identified [9] as a relevant comorbidity in the course of neoplastic, hepatic, cardiac, endocrinological or renal diseases, among others.

Sarcopenia is considered a multifactorial disorder [14] that is due to hormonal factors (decreases in growth hormone, insulin-like growth factor type I, vitamin D, testosterone and estrogen, increased myostatin, insulin resistance), nutritional factors (decrease in protein intake, micronutrient deficiency) and factors dependent on the musculoskeletal system (decrease in the number of muscle fibers, motor units, and alpha motor neurons), as well as factors related to the lifestyle (sedentarism, smoking habit) and with inflammatory processes (cytokines).

It is estimated that, currently, the majority of cases of sarcopenia are not diagnosed. Since universal disease screening cannot be considered, in practice it is recommended to carry out a case-finding strategy [10], that is, an opportunistic detection based on the active search for cases. This form of acting is especially relevant when give situations in which it is to be expected that there is a high prevalence of sarcopenia, such as advanced age and/or chronic diseases.

Now, there is no consensus on an operational definition of sarcopenia. However, the proposal of the European Working Group on Sarcopenia in Older People (EWGSOP), made in 2019 (EWGSOP-2 criteria) [15], are the most widely used. The EWGSOP-2 criteria establish the diagnosis of sarcopenia by the combination of low muscle strength (assessed by handgrip strength) and low muscle mass (assessed by DXA); physical performance (assessed by gait speed) categorizes the severity of the condition. Furthermore, the EWGSOP-2 criteria recommend the use of the SARC-F questionnaire [16], as an initial analysis measure, to find individuals with probable sarcopenia.

In IMRD, especially when they occur in elderly people, various factors that, such as functional disability and sustained inflammation can favor the appearance of sarcopenia [17]. In a systematic review [18] with meta-analysis, it was observed a correlation between CRP levels and the presence of the disease. Can et al. [19], through a cross-sectional study, showed that patients with sarcopenia they have higher levels of CRP and adiponectin, as well as a higher ESR. In another cross-sectional study, van Atteveld et al. [20] also observed inversely significant correlations between ESR and muscle strength, muscle mass, and physical function.

In the context of RA, studies on sarcopenia were initially preceded by research into cachexia [21, 22]. Although cachexia and sarcopenia share similarities, cachexia is primarily defined as a condition of involuntary weight loss due to chronic illness. To be diagnosed with cachexia [23], individuals must fulfill at least three of the following five criteria: diminished muscle strength, anorexia, fatigue, a low fat-free mass index, and irregular blood parameters such as inflammatory markers, albumin, and hemoglobin.

Over the last decades, the existing knowledge about sarcopenia in RA has gradually increased. It is now clear [24] that the risk of sarcopenia is elevated in patients with RA, and this condition is associated with a physical disability.

Several studies have shown a higher prevalence of sarcopenia in patients with RA compared to healthy controls [25, 26]. Most studies have been carried out using only the assessment of muscle mass (skeletal mass index, SMI) as a diagnostic criterion; in these cases, the frequency has ranged approximately between 20–40% [27]. When the analysis is conducted using the EWGSOP-2 criteria, the currently preferred definition, the values are somewhat lower [27–29].

The presence of sarcopenia in RA is related [30–33] to the age of the patients, disease duration, structural damage, disease activity, functional capacity, and treatment with glucocorticoids; the effect of biological therapy is controversial [30, 32].

Of interest, Shin et al. [33] have demonstrated than a wide spectrum of comorbidities was preferentially found among RA patients with sarcopenia than without, suggesting that sarcopenia is significantly associated with RA-related comorbidities, such cardiometabolic, pulmonary, and infectious diseases.

Moreover, a clear relation has been established in RA patients between sarcopenia and frailty, low bone mineral density, falls and fractures generating an amplification circle of disability linked to reduced mobility [34, 35].

The pillars on which the treatment of sarcopenia is based are exercise and diet [36]. The effect of exercise on muscle mass is the intervention with the most available information; resistance exercise training has a positive effect in terms of both bone gain and improvements in muscle mass and strength, circumstances that will result in an increased pace speed and coordination and a reduction in the number of falls. The existing knowledge about the effect of diet is much less; there is evidence of the beneficial effect of protein supplementation, omega-3 acids, and especially vitamin D.

There is no ongoing clinical trial specifically addressing the treatment of sarcopenia in patients with RA. To date, a combined intervention of exercise and nutrition has been the treatment of choice for older adults with sarcopenia [37].

Despite their prevalence and significant clinical impact, sarcopenia often remains underrecognized in the healthcare management of established RA. We agree with Bennett et al. [24] who, in a thorough review article, suggest that within a comprehensive care program, rheumatologists should maintain a high level of suspicion for this extra-articular manifestation. This approach will facilitate further investigations and interventions aimed at improving muscle health.

The growing complexity of RA management, coupled with the limited time available for patient interactions, presents a significant challenge in addressing this issue. The question arises as to how the current situation can be improved. A potential solution could involve a call to action by scientific societies, which might heighten rheumatologists' awareness of the problem. Nevertheless, forming a multidisciplinary alliance, including nurses and family doctors, offers a practical first step in tackling the challenges posed by this hidden comorbidity.

Abbreviations

EWGSOP: European Working Group on Sarcopenia in Older People

IMRD: immune-mediated rheumatic diseases

RA: rheumatoid arthritis

Declarations

Author contributions

JMN: Conceptualization, Visualization, Writing—original draft, Writing—review & editing.

Conflicts of interest

Joan M. Nolla, who is the Associate Editor of *Exploration of Musculoskeletal Diseases* and guest editor of the special issue "Comorbidities in rheumatoid arthritis" had no involvement in the decision-making or the review process of this manuscript.

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