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MINIREVIEWS

Association between sarcopenia and rheumatological diseases

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Abstract

Sarcopenia ("sarx" for muscle, "penia" for loss) is an important problem in the elderly. Although muscle loss is a part of natural aging, excessive loss that limits physical activity is considered pathological. Sarcopenia is associated with age, malnutrition, physical inactivity, inflammatory stress and hormonal changes. Although relationships between sarcopenia and various chronic inflammatory diseases have been shown, the role of rheumatologic disease in sarcopenia development is currently unknown. Our aim in this mini-review was to increase the awareness of clinicians to sarcopenia, and to evaluate studies in which the relationship between sarcopenia and rheumatologic diseases was investigated. We also aimed to determine whether the available literature was sufficient to confirm a strong relationship between these conditions. Although our findings showed that diseases such as rheumatoid arthritis, osteoarthritis and systemic sclerosis may have a role in sarcopenia development and progress, the methodologies and results of the majority of studies were insufficient in determining direct causal relationships. We believe future studies would benefit from focusing on the factors and causes of sarcopenia, with a goal of determining the factors associated with rheumatologic disease that are most effective in sarcopenia development.

Key words: Sarcopenia; Rheumatoid arthritis; Osteoarthritis; Rheumatologic diseases; Malnutrition; Chronic inflammatory diseases

Core tip: Although relationships between sarcopenia and various chronic inflammatory diseases have been shown, the role of rheumatologic disease in sarcopenia development is currently unknown. Our aim in this mini-review was to increase the awareness of clinicians to sarcopenia, and to evaluate studies in which the relationship between

sarcopenia and rheumatologic diseases was investigated. As stated many times, the literature on this topic is quite limited; however, available data may be sufficient to associate sarcopenia with chronic inflammatory diseases.

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INTRODUCTION

Sarcopenia is an important problem among elderly individuals. Approximately half of the population over the age of 80 is thought to have sarcopenia-related muscle loss[1]. This condition causes health problems, limits independence and increases morbidity and mortality due to an increased risk of falling[2,3]. Sarcopenia is thought to be highly associated with inflammatory stress, leading to muscle atrophy.

Rheumatologic diseases cause inflammation in various parts of the body, especially joints. As a result, these patients have severe joint pain, which limits their daily activity. Therefore, a significant association between sarcopenia and rheumatologic diseases could exist[4]. To date, only a handful of studies has explored the associations between rheumatologic disease and sarcopenia. Our aim was to evaluate the current literature on this topic and suggest future research directions.

SARCOPENIA

Sarcopenia was first described in 1988 by Rosenberg[5] as a reduction in bodily functions due to muscle mass depletion. The term is derived from two Greek words; "sarx" for muscle and "penia" for loss. In 2009, the International Working Group on Sarcopenia defined age-related sarcopenia as a loss of skeletal muscle mass and functions associated with aging. Later, the same group redefined the condition as "whole body or appendicular fat-free mass deficiency and combination of bad physical function"[6]. Due to this definition being insufficient in clinical practice, The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal mass, which can cause adverse consequences like physical disability, poor quality of life, and death[7].

Muscle mass is known to decrease linearly, beginning from the fourth decade of life. The rate of decrease is 8%-10% each decade until 70 years of age, and 15%-20% each decade thereafter[8-13]. Sarcopenia prevalence was found to be 14% among men aged < 70 years, 20% among men aged 70-74 years, 27% among men aged 75-80 years, and 53% among men aged > 80 years. This rate was 23%, 33%, 36% and 45% for the same age group of women, respectively[14]. However, previous research[15] stated that the prevalence of sarcopenia ranged from 5%-13% between the ages of 60-70, and between 11%-50% over the age of 80. These differences in the literature point to two important problems; firstly, the definition of sarcopenia can still be considered vague, and, secondly, clinicians may not be sufficiently aware of the condition.

In order to facilitate clinical practice, sarcopenia is divided into primary and secondary sarcopenia. Primary sarcopenia (also termed as age-related sarcopenia) develops due to ageing, while secondary sarcopenia is known to have various causes or triggers[16-19]. According to EWGSOP, sarcopenia is staged into three groups: presarcopenia, sarcopenia and severe sarcopenia. In presarcopenia, muscle mass is reduced, but muscle strength and physical performance are not affected. In sarcopenia, muscle mass as well as either muscle strength or performance is reduced. In severe sarcopenia, the reduction in muscle mass is accompanied by loss of both muscle strength and performance[7].

Although there are different recommendations for screening, elderly patients and/or patients with chronic illnesses like heart disease, patients whose history shows frequent falls, and those who are intentionally losing weight should be assessed for impairment in their daily activities[20]. EWGSOP has developed an algorithm for the detection of sarcopenic individuals in clinical and practical applications. According to their suggestions, the first step for sarcopenia diagnosis in

individuals over 65 years of age is to evaluate their physical performance with simple walking and hand-shake tests. If further evaluation is required, the Short Physical Performance Battery (commonly known as SPPB), a composite of various tests that determine the balance, gait, strength and endurance of patients, is applied. The tests used in the implementation of the SPPB and their details are not within the scope of this review; however, details of the test and other specifics may be found in the 2010 study authored by Cruz-Jentoft *et al*[7]. After physical performance is evaluated, the determination of muscle mass can be performed *via* various modalities that give similar results, including computed tomography, magnetic resonance imaging and dual energy X-ray absorptiometry[21,22].

At this time, there is no FDA-approved agent for the treatment of sarcopenia[23]. Although testosterone, estrogen, and growth hormone replacement therapies have been evaluated, they may not be beneficial due to the possibility of severe side effects[24-26]. Other options include myostatin and myostatin receptor inhibitors, androgen receptor modulators, herbal supplements, and omega-3 fatty acid supplements[20]. During the last two decades, a number of treatment strategies for sarcopenia have been developed[27]. Almost all strategies involve an increase in exercise levels, especially aerobic and resistance exercises, which can increase muscle strength[7,28]. Nutritional support has also been shown to be crucial in those who have low-protein diets[29]. Several studies have also shown the benefits of balanced high-protein diets (up to 1.5 g/kg·d protein) and supplementation with both essential amino acids and vitamin D[30-33].

SARCOPENIA AND RHEUMATOLOGIC DISEASE

Sarcopenia and rheumatoid arthritis

Sarcopenia has been associated with numerous risk factors, the most prominent of these factors being old age and alterations in both hormonal and inflammatory parameters, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (commonly known as ESR)[34-36]. Rheumatoid arthritis (RA) is a disease that causes chronic inflammation and reduction in physical activity[37,38]. Skeletal muscle index has been shown to be lower in patients with RA compared to healthy controls[39]. Furthermore, a recent study revealed an association between sarcopenia and diseases that cause chronic inflammation. Therefore, a close relationship between RA and sarcopenia may exist.

In one study[39], RA patients with sarcopenia were found to have higher CRP values than those without, even though there was no difference between these patients in terms of DAS28 (disease activity score for RA). A similar systematic review comparing RA and sarcopenia etiology found that lower bone mineral density was more common among RA patients with sarcopenia[40]. These findings show that RA patients may be predisposed to sarcopenia regardless of RA severity. In addition, various studies have reported that the pain-related reduction in physical activity among RA patients can result in the development and progress of sarcopenia[38,41,42]. For instance, a study authored by Munro *et al*[43] found that CRP and ESR levels were negatively correlated with muscle mass in a cohort of 97 RA patients. Furthermore, muscle loss in RA, "rheumatoid cachexia" defined as loss of muscle mass in the absence of fat tissue reduction, has been shown to occur in many patients with RA[44]. The effects of cachexia overlap with sarcopenia pathophysiology, and most patients with cachexia are sarcopenic[45]. Considering that muscle loss is the hallmark of sarcopenia, rheumatoid cachexia could explain the higher frequency of sarcopenia among RA patients.

Furthermore, inflammatory parameters, including those that are altered in RA (tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β), cytokines that tend to increase with age [interleukin 1 (IL-1) and interleukin-6 (IL-6)], have been associated with the development of sarcopenia[42,43]. However, the definition of sarcopenia was directly associated with muscle mass in both of these studies. Schaap *et al*[36] defined it as at least a 3% loss of muscle mass, while Ngeuleu *et al*[37] defined it as a reduction in relative skeletal mass index (< 5.5 kg/m^2 for women and < 7.26 kg/m^2 for men). In addition to population-based studies, it is known that cytokines, especially TNF-α and IL-6, stimulate protein catabolism in the muscle, leading to muscle loss. Thus, diseases with chronic inflammatory characteristics are thought to cause secondary sarcopenia, which exemplifies another association between RA and sarcopenia[46,47].

Although many of the aforementioned studies have reported significant associations between RA and sarcopenia in terms of etiology and laboratory/clinical findings, there are also studies that did not find any relationship[48]. The majority of studies that suggest a very close association between the two diseases have only

revealed associations between specific etiological factors and some clinical findings. Therefore, although it is tempting to conclude that RA and sarcopenia have a causal relationship (one way or the other), the literature is actually insufficient to draw such a conclusion. Further controlled studies, with the goal of determining which condition causes or leads to the other (preferably prospective studies or comparison of patients with early/long term disease), are required to confirm whether a causal relationship exists between the two diseases.

Sarcopenia and osteoarthritis

Osteoarthritis (OA) is associated with aging, chronic inflammation and obesity. Considering that aging and chronic inflammation are also factors for sarcopenia development and progress, a significant association between these two conditions may exist. Various studies have shown an association between the type of cytokines that increase during both conditions[49,50], while one study reported that OA and sarcopenia may potentiate each other's inflammatory activities through the production of pro-inflammatory agents[51]. Another important point is the fact that patients with OA have lowered physical activity, which may lead to muscle loss and sarcopenia[52,53].

A study by Kemmler *et al*[54] found that sarcopenia was more common in women with OA than those without. However, interestingly, muscle mass results were similar in both OA patients and those without arthritis. On the other hand, Toda *et al*[55] reported that reduced lower limb mass was frequent in patients with OA. This may suggest that the joints affected by OA are an important factor for the development of sarcopenia. Lower physical activity, especially in those with painful knee and hip joints, may translate to the exacerbation of muscle loss throughout the body, and could show a causal relationship between OA and sarcopenia[56]. This conclusion is supported by reports of lower skeletal muscle mass in patients with knee and hip OA[57,58]. However, it is important to keep in mind that the inflammatory condition brought about by sarcopenia could also both increase inflammatory burden in joints and increase OA severity. Current data are not sufficient to determine which condition causes or accelerates the other.

Therefore, it is apparent that current research has been unfruitful in determining whether sarcopenia is the cause or result of muscle problems in inflammatory diseases. Nevertheless, it is safe to say that a relationship between inflammatory stress and sarcopenia exists; however, further studies are required to determine the weight and direction of this relationship. Future studies that evaluate whether sarcopenia frequency is affected in those with inflammatory disease without joint pain (or the opposite) could potentially elucidate the nature of these associations.

Sarcopenia and spondyloarthropathies

Ankylosing spondylitis (AS) is a chronic inflammatory condition known to cause bone loss; however, muscle loss is not widely reported[59-61]. To our knowledge, only two studies suggest that muscle mass is reduced in those with AS. The first study[62] reported that patients with AS had significant reduction in lean body mass, while the second study evaluated muscle mass directly, and showed that both muscle mass and functional capacity were significantly reduced in patients with AS. The remaining studies showed no associations between AS and muscle mass[60,63]. While differences in measurement techniques and study design may cause variations in results, it is also crucial to keep in mind that AS primarily affects the vertebrae. Meanwhile, other joints are affected to a lesser degree, if at all. Thus, limitations in the movement of vertebrae may not be enough to accelerate or cause sarcopenia, even with increased inflammation.

One report[59] claims that patients with spondyloarthropathy had significantly lower muscle mass compared to controls. However, their findings showed a lack of association between changes in muscle mass and disease duration. This is an unexpected result, because if there was a strong relationship between the diseases, the findings of sarcopenia (muscle loss) should have worsened proportionately with disease duration. Therefore, we can conclude that the very limited literature on this topic does not confirm a positive relationship between spondyloarthropathy and sarcopenia.

Sarcopenia and other rheumatologic diseases

In a study comparing sarcopenia frequency among patients with chronic inflammatory diseases and non-inflammatory controls, patients with systemic lupus erythematosus were found to have significantly higher sarcopenia frequency than controls[4]. However, the definition of sarcopenia was accepted as unintentional loss of > 10 pounds of weight in the previous year, while weakness was defined separately. This definition is lacking in terms of determining whether the patient truly had

sarcopenia; however, considering that systemic lupus erythematosus patients may require high doses of corticosteroid therapy, the loss of muscle mass is to be expected. Future studies would benefit from correctly defining and evaluating sarcopenia with regard to steroid dose.

Muscle involvement is a very common finding in patients with systemic sclerosis (SSc), which may contribute to the development of sarcopenia. Although the literature is methodologically limited, many studies report that SSc patients have increased muscle loss, and sarcopenia is diagnosed in up to 20%–54% of these patients[64,65]. In a relatively larger study comprised of 61 SSc patients, it was reported that lean mass was significantly reduced in women with SSc. Furthermore, the same study showed that longer duration with SSc was associated with higher risk for sarcopenia[66]. The latter finding was also confirmed by Wang *et al*[67].

Psoriatic arthritis is another disease with chronic activation of inflammation, which primarily affects the skin in the form of lesions of varying severity. Fatigue is a common but underestimated feature of psoriasis; however, there was no association between psoriasis severity and fatigue severity, which may suggest that other factors lead to fatigue, such as sarcopenia development due to chronic inflammation[68]. A study by Krajewska-Włodarczyk *et al*[69] suggested that the quality of life of psoriasis patients was affected by fatigue, an underestimated and often overlooked clinical finding in psoriasis. Although the study did not directly evaluate sarcopenia, future studies may benefit from the evaluation of sarcopenia among patients with psoriatic arthritis, especially considering the association between inflammation and fatigue.

Although the majority of studies have not associated gout with sarcopenia, one large cross-sectional study found that the risk of sarcopenia was higher among gout patients[70]. In contrast, several studies have suggested that therapy for gout (allopurinol) could be protective against sarcopenia[71]. Allopurinol inhibits the enzyme xanthine oxidase, and has been shown to prevent the production of free radicals during muscle contraction[71]. Further studies are required to determine whether allopurinol can be used as a treatment in patients with sarcopenia.

Studies in this field have mostly focused on muscle mass in sarcopenic individuals. Although this approach is not entirely erroneous, it is important to remember that muscle mass evaluations may not capture the whole clinical picture in patients with sarcopenia, as these patients mainly suffer from reduced physical performance and muscle strength. Therefore, correctly defining sarcopenia in future studies will be of utmost importance in order to obtain accurate results. Furthermore, it is quite apparent that increased inflammation contributes to sarcopenia development. Therefore, sarcopenia research may benefit from better study designs that aim to discriminate between muscle strength and mass, while also taking into account the effect of inflammation on the condition. However, the available literature indicates significant associations between these inflammatory diseases and sarcopenia, a disease that causes significant morbidity and mortality. This finding, even by itself, can be considered as an important step in a field that has received insufficient attention.

CONCLUSION

As stated many times, the literature on this topic is quite limited; however, available data may be sufficient to associate sarcopenia with diseases such as RA, OA and SSc. Nevertheless, the analyses in the majority of these studies are not sufficient to support the existence of a causal relationship between the diseases. Additionally, we have observed that sarcopenia definitions in these studies did not conform to EWGSOP recommendations; therefore, the approach to sarcopenia diagnosis (and its definition) in these studies may have caused the differences observed in the results. Future studies should primarily focus on illuminating causal relationships between sarcopenia (with a correct definition) and rheumatologic diseases, and determining whether the presence of inflammation or the physical limitations brought by rheumatologic diseases are more critical in the development of sarcopenia.

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