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Clinical definition and diagnostic criteria for sarcopenia

Jun Udaka[1*], Norio Fukuda[2], Hideki Yamauchi[3] and Keishi Marumo[1]

[1] *Department of Orthopaedic Surgery, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan*
[2] *Department of Cell Physiology, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan*
[3] *Division of Physical Fitness, Department of Molecular Physiology, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan*

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Abstract The occurrence of sarcopenia and muscular dystrophy with aging has attracted attention. Many factors are reported as causes of sarcopenia, such as the functional decline of a digestive organ occurring with aging and malnutrition due to a decrease in food intake. Also, a decrease in growth hormone and an increase in cytokines are also considered to be causes of sarcopenia. Meanwhile, the differentiation between sarcopenia and disuse muscle atrophy is not clear. It will be important in future studies to clearly define the differences between sarcopenia and disuse muscle atrophy. Recently, the diagnostic criteria of sarcopenia have been defined according to a large-scale investigation. In the future, an easier sarcopenia diagnostic method should be developed. It is necessary to design specific treatment strategies more closely correlated to the clinical condition of individual patients, because the causes of sarcopenia vary widely. In this review, we summarize the characteristics of the clinical condition, diagnosis, and treatment of sarcopenia.

Keywords : muscle, atrophy, sarcopenia, diagnosis, therapy

Introduction

To date, muscular atrophy studies have focused mainly on disuse muscular atrophy using the immobilization and space-flight models[1,2]. This area of research has achieved success in the development of methods for the treatment and prevention of disuse muscular atrophy[3]. Recently, a new concept of muscular atrophy, sarcopenia, has received attention. The term sarcopenia was proposed by Rosenberg in 1989 to refer to muscle loss due to aging[4]. Aging societies, which have increased as a result of developments in medical technology, are thought to be the key reason for the attention to the concept of sarcopenia. Moreover, the high nursing care costs necessary to manage sarcopenia are a burden on medical economics[5]. Therefore, great effort has been initiated in order to establish the diagnostic criteria for sarcopenia[6]. Nevertheless, many questions remain regarding the clinical condition of sarcopenia.

Sarcopenia and disuse muscular atrophy share common characteristics[7,8], which has led to some confusion in the use of these terms[9]. Clear differentiation between these two conditions is therefore important for future research on sarcopenia. This paper summarizes the reports on sarcopenia and discusses the current status of sarcopenia diagnosis and treatment.

*Correspondence: judk@jikei.ac.jp

Causes of sarcopenia

Disuse muscular atrophy is a form of muscular atrophy that arises because of decreased muscular activity or motor stimulation. As sarcopenia is a form of muscular atrophy that accompanies aging, all of the changes that occur due to aging are considered to be causes of sarcopenia. It is reported that sarcopenia arises owing to a large number of factors[10,11] (Fig. 1), and these factors need to be investigated.

Muscular hypertrophy and atrophy result from muscle protein synthesis and breakdown, respectively. Therefore, a shortage of nutrients required for muscle protein synthesis hinders normal muscle metabolism. Consequently, environments in which nutrient intake becomes difficult facilitate the loss of muscle mass. The digestive tract in elderly people has a reduced ability to produce nitric oxide in the cardiac region, thereby lowering the ability of the region to expand. This results in a feeling of fullness even with the intake of only a small amount of food[12], which in turn reduces appetite, and can lead to a shortage of the amino acids necessary for muscle synthesis. Elderly people have also been shown to have a decreased

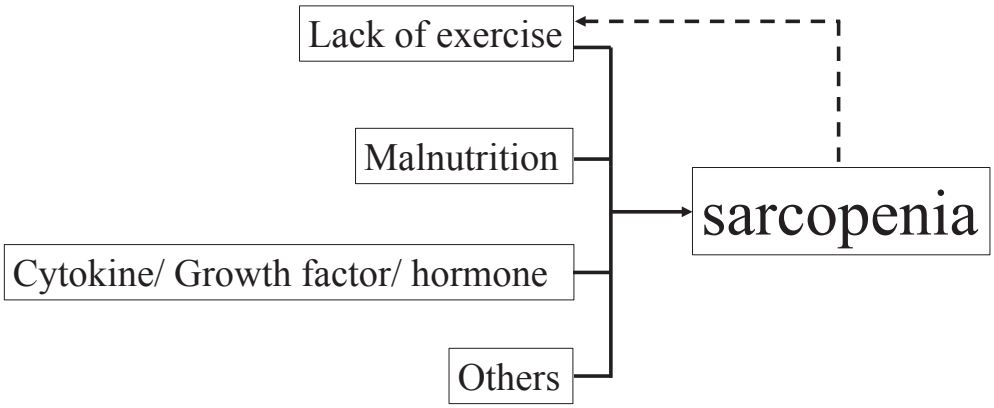

Fig. 1 Risk factor for sarcopenia. Sarcopenia is thought to progress by some risk factors occurring at the same time. Sarcopenia may accelerate lack of exercise.

ability to synthesize muscle protein from the amino acids they consume[13,14]. As such, elderly people who consume food rich in amino acids have been reported to have improved muscle protein synthesis. In particular, leucine has been shown to have a strong anabolic action on skeletal muscle[15,16]. The important role of vitamin D in muscle synthesis has also received attention. In fact, vitamin D intake has been reported to help prevent falls[17], which is thought to reflect increased muscle strength due to the action of vitamin D on muscle protein synthesis. Vitamin D receptor expression in skeletal muscle has also been shown to decrease with age[18]. The aforementioned results indicate an extremely important relationship between sarcopenia and nutrition.

The regenerative function of muscles has also been reported to be lower in patients with sarcopenia[19,20]. Satellite cells, which exist between the basement membrane and sarcolemma of muscle fibers, play an important role in muscle regeneration. When muscle is damaged, satellite cells are activated and begin to multiply in response to stimulation by growth factors and cytokines, and are transformed into muscle precursor cells. These cells merge with the existing muscle fibers to carry out muscle repair and hypertrophy. The decline in satellite cell function with age has been identified as one of the reasons for the decline in the ability of muscles to recover with age[21,22].

In addition, insulin-like growth factor 1 (IGF-1) and inflammatory cytokines have been reported to control the function of satellite cells. IGF-1, in addition to being secreted by the liver in response to growth hormones, it is also known to be produced within myocytes in response to mechanical stimulation[23,24]. IGF-1 binds with IGF-1 receptors on myocyte membranes, and phosphorylates the intracellular signal transduction pathway mediators, insulin receptor substrate 1 (IRS-1), phosphatidylinositol 3-kinase, and Akt. Phosphorylated Akt then promotes muscle protein synthesis via S6K and glycogen synthase kinase and the phosphorylation of forkhead box-O (FOXO), a transcription factor of atrophy-related genes (atrogenes). This hinders the intranuclear translocation of atrogenes and suppresses the breakdown of muscle protein[25,26]. However, FOXO proteins have been shown to accumulate in the nuclei of satellite cells in old age, suggesting that they are involved in the decline in growth functions[22].

Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are particularly important as causative factors of sarcopenia. TNF-α contributes to promoting skeletal muscle catabolism during cachexia[27]. Activation of NF-κB by TNF-α is known to decrease MyoD expression, which promotes the degradation of myosin[28]. Furthermore, activation of NF-κB by TNF-α increases the expression level of the MuRF1 gene. This promotes the degradation of muscle protein via the ubiquitin-proteasome system[29]. Meanwhile, IL-6 is secreted by macrophages and is known to decrease IGF-1 expression[30]. IL-6 can also activate NF-κB to promote skeletal muscle catabolism, and IL-6 production has been shown to be elevated in the elderly[31].

Changes in muscle type during atrophy

The skeletal muscle is divided macroscopically into red and white muscle tissues. The characteristics of muscle fibers can be further differentiated in detail through myosin ATP staining, myosin antibody staining, or myosin heavy-chain (MyHC) isoform quantification by electrophoresis[32,33]. Red muscle tissue is mainly composed of type I fibers, and white muscle tissue type II fibers. Type I fibers have slow contraction speeds and are thus called slow-twitch fibers, while type II fibers have fast contraction speeds and called fast-twitch fibers. For instance, the soleus has many type I fibers, whereas the gastrocnemius has many type II fibers. The muscle fiber type is known to change during atrophy according to the causes that trigger the atrophy. For example, disuse muscular atrophy that arises according to the fixed-joint or dangling hind-leg model exhibits a decrease in type I fibers and an increase in type II fibers[34,35]. MyoD and HMGCoA-reductase inhibition have been suggested to participate in myosin

heavy chain (MyHC) changes[36,37]. However, unlike disuse muscular atrophy, in sarcopenia, the type II fibers are known to be susceptible to influence[10,38,39]. This reduces the muscle contraction speed, causing loss in the ability to execute the rapid movements needed to protect against falling. This chain of pathological events is thought to be one of the causes of falls in elderly people[17]. Elucidating the cause of atrophy which is selective for a specific muscle type could play an important role in treating sarcopenia.

Mitochondrial changes that accompany muscular atrophy. Adenosine triphosphate (ATP) is the energy source for muscular contractions. Muscles contract using chemical energy from the release of inorganic phosphate (Pi) during ATP hydrolysis. ATP is a chemically unstable substance that cannot be incorporated directly from outside the cell or stored for long periods inside the cell. Thus, ATP is synthesized as necessary by myocyte mitochondria. Meanwhile, oxidative stress has been reported to increase in muscle tissue when activity is restricted, such as when immobilized in a cast or splint[40]. In sarcopenia, this is thought to increase the generation of active oxygen in mitochondria, which increases the damage to muscle tissue[41]. Therefore, mitochondrial dysfunction can have a considerable effect on myocytes. In fact, the amounts of mitochondria[42] and neutralizing enzymes for the generation of active oxygen in mitochondria are reported to decline in disuse atrophy[43]. A reduced ability of mitochondria to synthesize proteins and lower enzyme activity levels was also reported in sarcopenia[44]. These changes may be factors that influence the functional decline in myocytes that accompanies aging. A recent study suggested that mitochondrial function disorders and insulin resistance affect the onset of sarcopenia[45]. In relation to this, angiotensin II receptor blockers (ARBs), hypotensive agents, have been reported to increase skeletal muscle mass[46], which is thought to be due to the activation of mitochondrial function by ARBs[47].

Relationship between muscular function and changes to sarcomeric structure

The decrease in muscular cross-sectional area that accompanies atrophy has a considerable effect on the reduction in muscular tension, because muscle strength is proportional to the cross-sectional area of the muscle. In muscular atrophy, muscle force per unit of cross-sectional area is also decreased. This indicates the presence of factors that regulate muscular force other than muscular cross-sectional area. Possible causes for this are the expansion of the space between thick and thin filaments in the sarcomere (lattice spacing), a decrease in the number of filaments, and shortened filament length[43,48,49]. In our experiments on the effect of lattice spacing on reductions in contractile force, we found that improving lattice spacing significantly increased contractile force, although this was still less than that in healthy muscle. This suggests the presence of factors that regulate contractile force other than the muscular cross-sectional area and lattice spacing of filaments[35].

The basis for the expansion in lattice spacing is thought to be the stabilizing effect of connectin (titin) on the sarcomeric structure. This protein is known to act as a "spring" during muscular extension[50,51]. The decrease in connectin that is observed in atrophy reduces this spring-like function, which is thought to destabilize the function that maintains thick filaments in their location, causing lattice spacing to expand. In addition to connectin, intermediate filaments, such as desmin, have been reported to be important factors in regulating muscular structure[52]. Future research is expected to clarify how these multiple factors help determine the structure of the sarcomere. Few reports have been published on microstructure in sarcopenia[53]. However, as the functional irregularities that arise in sarcopenia are clarified, more detailed structural analyses are needed.

Diagnosis and treatment for sarcopenia

Many studies have examined the pathology of sarcopenia, yet the clinical reports are few. In particular, diagnostic methods have not been standardized. Muscle mass measurement using dual-energy X-ray absorptiometry (DXA, or formerly DEXA) is the most commonly used method for diagnosing sarcopenia[54,55]. Bioelectrical impedance analysis (BIA) is a simple method that has also been used despite its lack of accuracy. While imaging diagnostic modalities such as magnetic resonance imaging (MRI) or computed tomography (CT) allow for accurate measurements of muscle mass, these methods are cost prohibitive[56-58].

Considering, however, that these diagnostic methods do not necessarily reflect the patient's motor abilities, the European Working Group on Sarcopenia in Older People (EWGSOP) developed a method of diagnosis that focuses on motor abilities[6]. They proposed a cutoff walking speed of 80 cm/s for sarcopenia diagnosis, and recommended additional examinations such as DXA or bioelectrical impedance analysis (BIA) for patients with walking speeds that fall below the cutoff value. After this report was published, clinical surveys on sarcopenia similar to that of the EWGSOP were undertaken in other regions as well[59-61]. However, because this cutoff value is a European criterion, it will be necessary to clarify whether this value is appropriate for implementation in other regions as well.

The relationship between biomarkers and sarcopenia has been reported[57,58,62], and the usefulness of measuring several biomarker candidates, including inflammatory biomarkers, clinical parameters, hormones, and products of oxidative damage, has been studied. Biomarkers that can be obtained from blood and urine may be beneficial,

Table 1. Diagnostic method for sarcopenia

Physical performance	Short Physical Performance Battery (SPPB) Repeated Chair Stands Balance Test Walking speed grip strength	Established tool for elderly people and rehabilitation
Imaging	DEXA BIP CT, MRI	Established tool High cost
Others	Biochemical markers (IL-6, TNF-α, IGF-1, etc)	Unestablished tool

as there is little burden on the patient. Considering that sarcopenia occurs as people age, the potential patient population is extremely large. Therefore, performing imaging diagnostics for all patients would be problematic from the standpoint of health economics. However, at present, no large-scale clinical trials use biomarkers for sarcopenia diagnosis (Table 1).

A variety of approaches have been undertaken to treat sarcopenia[63-65]. Strength training is known to significantly increase both muscle mass and strength in the elderly[66,67]. Studies have also indicated that nutritional interventions are important. However, their effects are considered insufficient compared to that of exercise. Taken together, robust prescriptions of both nutrition and exercise have been reported to achieve even greater results[68] Owing to the multiplicity of the causes of sarcopenia, any one therapy alone is unlikely to achieve a satisfactory effect. Recent studies have suggested that an exercise effect can be achieved through medication[69,70]. Such drugs could prove effective in patients who are not able to perform sufficient exercise for therapeutic purposes. Nevertheless, as can be expected, the use of an exercise pill to address obesity or lack of exercise has been criticized[71].

Conclusion

Sarcopenia has many causes. The mechanism by which each cause influences the onset of the disease is in the process of being elucidated. Clarifying the differences between sarcopenia and disuse muscular atrophy would likely help establish better methods of diagnosis, which could also lead to personalized treatment.

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