Sarcopenia: Definition, Epidemiology, and Pathophysiology

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INTRODUCTION

In 1988, Irwin Rosenber proposed that sarcopenia is age related decrease of skeletal muscle mass (SMM) and function.[1] The term sarcopenia is still largely unknown among clinicians and researchers. It is usually accompanied by physical inactivity, decreased mobility, slow gait, and poor physical endurance which are also common features of the frailty syndrome.[2] Moreover, aging and physical disability are also related to an increase in fat mass, particularly visceral fat,[3] which is an important factor in the development of metabolic syndrome and cardiovascular disease (CVD).[4] Therefore, sarcopenia with obesity in the elderly may synergistically increase their effect on metabolic disorders, CVD and mortality as well as physical disability.[5]

A progressive loss of muscle mass occurs from approximately 40 years of age. This loss has been estimated at about 8% per decade until the age of 70 years, after which the loss increases to 15% per decade.[6] A 10-15% loss of leg strength per decade is seen until 70 years of age, after which a faster loss, ranging from 25% to 40% by decade, occurs.[7,8] It is estimated that a 10.5% reduction of the prevalence of sarcopenia could lead to a reduction of healthcare costs by 1.1 billion US dollars per year in the United States.[9] Korea is rapidly aging. According to the Korea National Statistical Office, 7.2% of the Korean population was aged 65 and older (i.e., elderly) in 2000. The percentage is expected to rise to 19.1% in
2025 and 34.4% in 2050.[10] The speed at which Korea is becoming an aged society is unprecedented among developed countries. Research regarding the impact of sarcopenia is essential for the development of public health programs for the increasingly elderly Korean population.

The prevalence of sarcopenia was found to vary substantially.[11] The prevalence and measurable impact of sarcopenia depends crucially on how sarcopenia is defined. A proper definition is the necessary base for clinical diagnosis and development of tailored treatment. In addition, many explanations for sarcopenia have been proposed metabolic effects such as reduction in anabolic hormone productions or sensitivity, dysregulation of cytokine secretions, and inflammatory state. However, little is known about the association between various indices of sarcopenia and metabolic parameters.

The aim of the present review is to summarize the main operational definitions of sarcopenia and describe the different methods assessing sarcopenia, together with results from Korean sarcopenic obesity study (KSOS) that we performed. We will also focus on metabolic considerations in applying sarcopenia in the clinical practice.

1. Definitions of sarcopenia based on SMI

1) Operational definitions of sarcopenia based on SMI

The most commonly used, low cost and accessible methods to assess SMI include dual energy X-ray absorptiometry (DXA), anthropometry and bioelectrical impedance analysis (BIA). Magnetic resonance imaging (MRI), computerized tomography (CT) and creatinine excretion are the most specific standards for assessing muscle mass or cross sectional muscle area. Table 1 summarizes each of these measurement methods. Baumgartner et al.[12] were the first to develop a definition of sarcopenia with DXA. DXA is a well-defined technique for analyzing body composition and currently the procedure of choice for routine assessment of bone mineral density. Based on studies showing that amount of appendicular SMI (ASM) could be estimated by using the bone-free and fat-free mass of the arms and legs as assessed with DXA.[13,14] Furthermore, analogous to the body mass index (BMI), the ASM was devised by height squared (ASM/height²) to adjust for the strong association between body height and ASM. To define the cut-points for low ASM an approach similar to that of osteoporosis was taken. They defined Sarcopenia as reduction in ASM/height² of two standard deviations (SD) or more below the normal means for a younger reference group. In our study, for men, the cut-off values for sarcopenia were 7.40 kg/m² defined as less than two SD below the sex-specific normal mean for the young reference group. For women, the corresponding limits were 5.14 kg/m². Their values are detailed in Table 2.

Second definition of Sarcopenia was developed by Janssen and colleagues.[15] They measured SMI (%; total SMI [kg]/weight [kg] × 100) using BIA. Again, analogous to the osteoporosis definition, an index less than two SD from the sex-specific mean value of a young reference group was considered to indicate class II sarcopenia. An index within one to two SD from the young reference group was considered class I sarcopenia.

A third approach to define sarcopenia is the use of residual method developed by Newman et al.[16] The residual method was defined as the reference values of sex-specific lower 20% of the distribution of residuals between measuring techniques for sarcopenia

Table 1. Measuring techniques for sarcopenia

| Measuring techniques | Measurements | Comments |
|----------------------|--------------|----------|
| Muscle size          | Total skeletal muscle mass | Reliable, low radiation exposure |
| DXA scan             | Tissue conductivity | Less reliable |
| BIA                  | Muscle cross-sectional area | Radiation exposure, expensive |
| CT scan              | Muscle cross-sectional area | Expensive, less available |
| MRI scan             | Lower extremity function | Validated tool for older people |
| Physical performance |                          |          |
| SPPB                 |                          |          |

CT, computed tomography; MRI, magnetic resonance imaging; BIA, bioelectric impedance analysis; DXA, dual energy X-ray absorptiometry; SPPB, short physical performance battery.
sured ASM and the ASM predicted by linear regression analysis used to model the relationship between ASM as a dependent variable, and age, height (meters) and total fat mass (kg) as the independent variables. A positive residual indicates a relatively muscular individual, whereas negative residual is indicative of a relatively sarcopenic individuals.[17]

Fourth, although the high cost and operational complexity limit use of MRI and CT in large clinical trials, they considered the most accurate imaging methods to assess muscle mass, muscle cross-sectional area (CSA), and muscle quality as determined by muscle density and intramuscular fat infiltration. Visser et al.[18] showed that smaller mid-thigh muscle area using CT was associated with poorer lower extremity performance in well-functioning older men and women. Since thigh muscle CSA showed a strong association with body weight than with body height, thigh muscle CSA was corrected by body weight (CSA/weight), as a sarcopenic index of weight burden thigh muscle mass.[19] Sarcopenia was defined as thigh muscle CSA/weight within 1 SD value of the CSA/weight distribution in a young reference group for both men and women.[20]

2) Operational definitions of sarcopenia based on SMI and muscle strength and function
Muscle strength does not depend solely on muscle mass, and the relationship between strength and mass is not linear.[8,21] Therefore, from the initial definition of ‘age-related loss in skeletal muscle’, sarcopenia subsequently evolved to current operative definitions simultaneously capturing both quantitative (i.e., muscle mass) and qualitative (i.e., muscle strength and function) declines. The European Working Group on Sarcopenia in Older People (EWGSOP, the Sarcopenia Working Group) proposed the definition based on an algorithm based on the preliminary screening of low gait speed (threshold established at $\leq 0.8$ m/s) and low handgrip strength (lowest quartile of sample distribution). [22]

A clinical definition of sarcopenia ought to use methods of assessment that are valid, reliable, specific to skeletal muscle, predictive of future health events, non-invasive, practical, low cost and widely accessible. In this respect, sarcopenia expressed as muscle quality assessed by means of a combined measure of muscle mass with DXA and measure of grip strength with a hand-held dynamometer seems a very promising approach, as both these methodologies share most of the abovementioned characteristics.

2. Epidemiology of sarcopenia
The epidemiological trends that characterize our generation are an obesity epidemic and the aging of the population.[23] Aging results in sarcopenia, which is Greek for ‘poverty of flesh’. [24] Although all men and women experience some degree of sarcopenia, this is variable and on a continuum. However, in a similar fashion to bone mineral density scores for osteoporosis, it is possible to dichotomize this continuous process by establishing a lower limit of normal such as two SD below the mean index of muscle mass for healthy young adults. First, when Baumgartner et al.[12] used a cut-off point of two SD for ASM/height² in the young reference group to define sarcopenia, the prevalence of sarcopenia ranged from 13 to 24% in persons aged 65 to 70 years and was over 50% for those older than 80 years. In this study, the prevalence was higher for men over age 75 years (58%) than for women (45%).[12] In a similar study, the prevalence based on total skeletal mass determined by DXA was 10% for men and 8% for women between 60 and 69 years and 40 and 18%, respectively, for men and women over 80 years.[25] Although sarcopenia most specifically refers to loss of SMI, clearly, functional ability is especially important in elderly men and women. It would be certain that a relationship should exist between muscle mass, strength, and the ability to carry out functional tasks. This was evident in the New Mexico study in which sarcopenic women had 3.6 times higher rates of disability and men had 4.1-fold higher rates compared with those with greater muscle mass.[12] However, ASM/height² index is highly correlated with BMI as current criterion of obesity.[16] Thus, this index primarily identified thin people as sarcopenic and could have limited applications for underestimating sarcopenia in overweight or obese subjects.[17] To overcome this limitation, Newman et al.[16] and Delmonico et al.[17] proposed new criteria for sarcopenia based on the amount of lean mass being lower than expected for a given amount of fat mass using residuals from linear regression models. In addition, Janssen et al.[15] proposed a definition of sarcopenia as SMI of one or two SD below the mean for a younger reference group. They reported a higher prevalence of more severe sarcopenia in women compared with men over 60 years.[15]
These researchers found that the likelihood of functional impairment and disability was approximately two times greater in the older men and three times greater in the older women with severe sarcopenia than in the older men and women with a normal SMI, respectively.

There have been few studies evaluating the association between sarcopenia and metabolic disorders including atherosclerosis. In addition, little is known about the association between sarcopenic obesity, metabolic alteration and health status. In the cross-sectional analysis of the New Mexico Aging Process Study, subjects with sarcopenic obesity did not show a higher incidence of congestive heart disease or hip fracture. Moreover, the prevalence of metabolic syndrome was highest in the non-sarcopenic obese group, followed by the sarcopenic obesity group, and normal group, and was lowest in the sarcopenic non-obese group.[26] Similarly, in obese postmenopausal women, sarcopenia appeared to be associated with lower CVD predisposing risk factors.[27] Like these, several previous epidemiologic studies failed to find the association between sarcopenic obesity and cardiovascular risk factors. Defining sarcopenic obesity by different indices such as ASM/height\(^2\) and SMI, Authors explored the relationship between sarcopenic obesity and metabolic syndrome in a large sample of Korean adults.[28] Authors estimated the prevalence of sarcopenia and sarcopenic obesity in Korean men and women and found considerable differences in prevalence for sarcopenia and sarcopenic obesity depending on the definitions of each that are used (Tables 3, 4). Although the prevalence of sarcopenic obesity defined using two or more SD of ASM/height\(^2\) index in our study population is lower than that reported in Caucasian populations, the prevalence of sarcopenia and sarcopenic obesity

| Indices of sarcopenia | ASM/height\(^2\) below 2 SD (Baumgartner et al.) | Residual 20th percentile (Newman et al.) | SMI Below 2 SD (Janssen et al.) |
|----------------------|-----------------------------------------------|----------------------------------------|--------------------------------|
| Men                  |                                               |                                        |                                |
| 40-59 yr (n=72)      | 2.8                                           | 19.4                                   | 1.4                            |
| ≥ 60 yr (n=79)       | 6.3                                           | 15.4                                   | 5.1                            |
| Women                |                                               |                                        |                                |
| 40-59 yr (n=120)     | 2.5                                           | 15.1                                   | 4.2                            |
| ≥ 60 yr (n=121)      | 4.1                                           | 22.3                                   | 14.2                           |

ASM, appendicular skeletal muscle mass; SD, standard deviations; SMI, skeletal muscle index.

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| Indices of SO | -2SD of ASM/height\(^2\) plus Median of total body fat percentage (Baumgartner et al.) | 2 lower quintile of ASM/height\(^2\) plus 2 higher quintile of total body fat percentage (Zoico et al.) | -2SD of SMI plus 2 higher quintile of total body fat percentage (Kim et al.) |
|--------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Men          |                                                                                   |                                                                                                 |                                                                     |
| 40-59 yr (n=72) | 2.8                                                                               | 9.7                                                                               | 1.4                                                                    |
| ≥ 60 yr (n=79) | 1.3                                                                               | 20.3                                                                              | 5.1                                                                    |
| Women        |                                                                                   |                                                                                                 |                                                                     |
| 40-59 yr (n=120) | 0.8                                                                               | 11.8                                                                              | 3.3                                                                    |
| ≥ 60 yr (n=121) | 0.8                                                                               | 16.5                                                                              | 12.5                                                                   |

ASM, appendicular skeletal muscle; SMI, skeletal muscle index; SD, standard deviation; SO, sarcopenic obesity.

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using alternative methods, such as SMI index and residuals, is similar. Authors also found a significant association between SMI quintile and metabolic syndrome. KSOS study showed that subjects with sarcopenic obesity, identified using the SMI index, were more likely to have metabolic syndrome (Fig. 1).

Because SMI and total body fat are closely correlated, an increase in SMI is often accompanied by gain in total body fat.[16] Therefore, assessment of the effect of sarcopenia on metabolic syndrome and atherosclerosis might require simultaneous consideration of visceral obesity. In addition, although sarcopenia and visceral obesity may potentiate each other, resulting in a substantial effect on metabolic disorders and atherosclerosis in older persons, most studies thus far have investigated the role of sarcopenia and visceral obesity separately. Therefore, authors presented a new surrogate index of sarcopenic obesity using the ratio of ASM-to-visceral fat area (VFA) that we call muscle-to-fat ratio (MFR). Authors further examined the association between MFR, components of metabolic syndrome, and arterial stiffness in an apparently healthy general population.[29] MFR was independently associated with metabolic syndrome and arterial stiffness even after adjusting for other risk factors. Longitudinal study results are needed to investigate the effects of sarcopenia and sarcopenic obesity on chronic metabolic disorders and CVD in older individuals.

3. Pathophysiology

Skeletal muscle consists of two types of fibers. Type II fast fibers have a higher glycolytic potential, lower oxidative capacity, and faster response as compared to type I slow fibers. The type I fibers are known as fatigue-resistant fibers due to their characteristics that include greater density of mitochondria, capillaries, and myoglobin content. Most muscles consist of both types of fibers except for postural muscles, consisting of type I fibers only. During slow, low intensity activity, most strength generated comes from type I fibers, while in high intensity exercise strength comes from type I and II fibers. With age, atrophy almost only affects type II fibers.[30]

Many explanations for sarcopenia have been proposed such as neurodegenerative process, reduction in anabolic hormone productions or sensitivity, dysregulation of cytokine secretions, modification in the inflammatory state (Fig. 2).

1) Neuromuscular aging

Neuron loss is a progressive, irreversible process that increases with age.[31] Age-related neurodegeneration may contribute importantly to the effects of age on muscle. Multiple levels of the nervous system are affected by age, including the motor cortex, the spinal cord, peripheral neurons, and the neuromuscular junction. Within the spinal cord, there is a substantial decline in the number of alpha motor neurons, and there may be a preferential loss in those motor neurons supplying fast motor units. Other reports have noted age-related losses in peripheral nerve fibers and alterations of their myelin sheaths. Finally, age-related changes have been noted in the neuromuscular junction, with reduced number but increased size of terminal areas and a reduction in the number of synaptic vesicles.[32-34] These findings, taken together with muscle morphological changes consistent with a chronic neuropathic process, as an important contributing factor to reduced muscle fiber number and muscle mass.[35,36]

2) Age-related changes in hormones levels and sensitivity

Maintenance of SMI requires that the rate of synthesis is in balance with the rate of degradation. Over time, imbalance can result in severe muscle loss. Aging is associated with modifications of hormones production and sensitivity especially with regard to growth hormone (GH)/insulin-like growth factor-I (IGF-1), cortisosteroids, androgens, es-
trogens, insulin. These hormones may influence the anabolic as well as the catabolic state for an optimal muscle protein metabolism.[37] A decrease in GH/IGF-1 levels is frequently demonstrated in elderly people[38] and this is paralleled by changes in body composition, i.e., increased visceral fat and decreased lean body mass and bone mineral density. Thus it was tempting to treat patients suffering from muscle loss by GH injections but no evidence of increased muscle strength was reported even if an increased muscle mass may occur.[39,40] On the contrary, side effects occurred frequently.[40]

Aging is associated with low testosterone which may lead to decreased muscle mass and bone strength, and thereby to more fractures and complications. Testosterone has proven effects to increase muscle mass and muscle function, but along with these beneficial effects, there are also problematic side effects.[41]

Increased visceral fat, and decreased lean body mass and bone mineral density are seen in the state of hypercortisolism. Increasing age has been shown to be associated with elevated evening cortisol levels in men. An increased exposure of several tissues to glucocorticoids with aging, i.e., visceral fat cells, in combination with the reduction of the lipolytic effects of declining GH levels, may contribute to the age-dependent increase of visceral fat accumulation.[42]

It is now very well established that low levels of blood vitamin D levels are associated with decreased muscle strength, but vitamin D supplementation results are still under investigation. Visser et al.[43] reported that lower 25-hydroxyvitamin D (25(OH)D) levels increase the risk of sarcopenia in older men and women. In addition, 25(OH)D levels were positively associated with SMI in our previous study.[44] Low 25(OH)D levels may be associated with both sarcopenia and low physical activity. Moreover, given the beneficial results of calcium + vitamin D supplementation on bone function,[45] it is expected that correcting vitamin D levels will also be beneficial for muscle function.

Finally, in older individuals, skeletal muscle protein synthesis is resistant to the anabolic action of insulin.[46] Therefore, insulin resistance may be associated with age-related muscle loss, also called sarcopenia. Inversely, loss of skeletal muscle, which is the largest insulin-responsive target tissue, may produce insulin resistance that promotes CVD and other metabolic disorders. Sayer et al.[47] reported that decreased grip strength was significantly associated with homeostasis model assessment of insulin resistance (HOMA-IR) as well as with increased odds of having metabolic syndrome. HOMA-IR levels were negatively correlated with SM and positively correlated with VFA in our previous study.[44] In addition, Park et al.[48] found that type 2 diabetes is associated with accelerated loss of muscle strength and mass in a 3-year follow-up of the Health ABC study. Also, authors recently reported that type 2 diabetes was associated with an increased risk of sarcopenia, and that these characteristics may contribute to physical disability and metabolic disorders in older adults with diabetes.[49]

3) Age-related changes in inflammatory factors

Increased circulating levels of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1, and C-reactive protein (CRP) are seen in the elderly.[50] It is now established that adipose tissue is an active endocrine organ that secretes hormones and cytokines that affect systemic inflammatory status. Either adipocytes or infiltrating macrophages in adipose tissue produce adipokines and proinflammatory cytokines, such as IL-6 and TNF-α, which induce the production of CRP in the liver. Honda et al.[51] found that protein-energy wasting is common in overweight end-stage renal disease patients and is associated with inflammation. Using cross-sectional data from the InCHIANTI study, Schrager et al.[52] found that obesity directly affects inflammation, which in turn negatively affects muscle strength. Furthermore, Stenholt et al.[53] found that the combination of high body fat percentage and low hand grip strength is associated with increased levels of CRP. In our previous study, which examines an Asian population, high-sensitivity (hs)-CRP levels were significantly and independently associated with sarcopenic obesity, even after adjusting for several other risk factors.[44] Therefore, low-grade inflammation might be one of the principal factors involved in the vicious cycle of sarcopenia and obesity in the elderly.

4) Role of myokines in muscle-fat crosstalk

Skeletal muscle is an endocrine organ, which by secretion of hormone-like factors may influence metabolism in tissues and organs. Analogous to the adipokines, cytokines and other factors secreted from adipose tissue, muscle-derived proteins are called myokines.[54,55] The first muscle-derived secreted protein to be described was the cytokine
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IL-6. Today, it is clear that many additional signaling molecules are produced by contracting muscle fibers and the current list of myokines includes IL-6, IL-8, IL-15, brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), follistatin-like 1 and fibroblast growth factor-21 (FGF-21).[54-57] Myokines act in an auto-, para- or endocrine fashion and thereby have major implications on metabolic and other properties of muscle as well as distal organs. IL-6 induces glucose uptake and fatty acid β-oxidation in muscle, stimulates hepatic gluconeogenesis and induces lipolysis in fat.[54] Similarly, IL-15 seems to be involved in muscle-adipose tissue crosstalk.[54] High local IL-8 concentrations might be involved in exercise-induced angiogenesis and hence increased capillarization of skeletal muscle.[54] BDNF augments fatty acid β-oxidation in muscle and might contribute to the muscle-brain crosstalk in exercise.[54] Under conditions of obesity, secretion of adipokines from adipose tissue is abnormal, and this cytokine imbalance contributes to the development of cardiovascular and metabolic diseases. Skeletal muscle may secrete myokines that confer some of the protective properties of exercise.[56] As such, these myokines would oppose the harmful effects of the pro-inflammatory adipokines that are expressed in the obese state (Fig. 3).

5) Sarcopenic obesity
Muscle mass loss in the elderly is associated with an increased fat mass. The imbalance between SMI and visceral fat mass in older individuals occurs even in the absence of significant changes in BMI and may have synergistic effects on health outcomes including metabolic disorders and mortality.[5,58] These imbalances are extreme in some individuals, producing a condition that is a combination of obesity and sarcopenia, a condition recently termed “sarcopenic obesity”. It is likely that the loss of muscle mass (sarcopenia) and reduced strength (dynapenia) cause reduced physical activity during aging.[59] Reductions in muscle mass and physical activity levels decrease total energy expenditures, which results in the accumulation of fat mass, especially visceral fat.[24,60] Along with visceral fat accumulation, loss of skeletal muscle, which is the largest insulin-responsive target tissue, produces insulin resistance which promotes metabolic syndrome. Moreover, increases in visceral fat may lead to higher secretion of pro-inflammatory adipokines that further promote insulin resistance as well as potentially direct catabolic effects on muscles.[52,61] Thus, a vicious circle between muscle loss and fat gain changes in body composition may lead to more sarcopenia and then to further metabolic problems and inflammation.[58] Authors found a significant association between SMI quintile and metabolic syndrome.[28] Our previous study also showed that subjects with sarcopenic obesity, identified using the SMI index, were more likely to have metabolic syndrome.[28]

4. Perspectives and Conclusions
Age-related sarcopenia is common and has huge personal and financial costs. Sarcopenia is a mystery for medicine, and despite the numerous publications available in the literature and the number of papers currently being published, there is no agreement about its definition, and even less about its main causes. Which reference populations should be used to decide whether the amount of muscle mass is normal or abnormal? Concerning osteoporosis, cut-off points are based on the optimal combination of sensitivity and specificity to determine the occurrence of fractures. In case of osteoporosis the risk of fractures is used as clinical outcome parameter. For Sarcopenia, a clear clinical outcome is still lacking. In addition, for sarcopenia it is crucial to define reference groups, based on gender, ethnicity and race.

Although the amount of muscle mass is associated with muscle strength,[21,61] there is accumulating evidence that muscle mass and muscle strength are two different entities.[59] Therefore, Clark et al.[59] proposed the term...
Dynapenia to define the age-related loss of muscle strength in 2008. Dyna refers to “power, strength, or force” and penia refers to “poverty.” The clinical consequences of dynapenia are significant, because it increases the risk for functional limitations, disability, and mortality. Future work originating from many scientific disciplines, e.g., epidemiology and physiology, is required to provide the fundamental knowledge needed to eventually develop effective interventions to prevent and treat dynapenia.

Besides a generator of strength, muscle tissue is an important organ performing protein storage, glucose regulation, hormone production and other cellular mechanisms. In addition, skeletal muscle has been identified as an endocrine organ due to its capacity to produce and secrete myokines and other proteins. Moreover, the metabolic effects of sarcopenia including a decrease in resting metabolic rate and reduction in physical activity, may lead to an increase of fat mass, particularly visceral fat. Visceral obesity directly affects inflammation and insulin resistance and may cause functional limitation, which in turn negatively affects SMI, contributing to the development and progression of sarcopenic obesity. Therefore, sarcopenia and obesity may potentiate each other and have a synergistic effect on physical capacity, chronic metabolic disorders and CVD. However, previous researches on these synergistic effects are not clear. Although authors introduced MFR (an index of SMI corrected by visceral obesity) was independently associated with metabolic syndrome and arterial stiffness,[29] further study results are needed to investigate effects of sarcopenic obesity on chronic metabolic disorders and CVD in older individuals.

In conclusion, a clinically more relevant approach to define sarcopenia should be based on cutoff points of muscle mass or muscle quality levels determined by expert consensus according to the risk for future health-related events, such as mortality, physical disability, or metabolic disorders. Therefore, the ultimate goal is to identify dietary and exercise strategies, lifestyle changes and treatments that can prevent or delay the onset of sarcopenia. In addition, in future studies, the concept “sarcopenic obesity” deserves more attention as well as the role of muscle quality aspects.

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