Chapter 12
Sarcopenia: Current Topics and Future Perspective

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Abstract Sarcopenia, which is an age-related loss of skeletal muscle mass and muscle weakness, is a disease that is currently attracting attention due to its high prevalence and significant impact on adverse health outcomes. Several international working groups have reported diagnostic criteria for sarcopenia, and it is now common to diagnose sarcopenia based on skeletal muscle mass, muscle strength, and physical performance. As countermeasures, resistance exercise and protein (amino acid) intake are recommended, as these have been shown to increase skeletal muscle mass, increase muscle strength, and improve physical function. We expect that more substantial basic and clinical research will be conducted in the future so that more appropriate management strategies for sarcopenia can be implemented.

Keywords Sarcopenia · Muscle mass · Muscle strength · Exercise · Nutrition

12.1 What Is Sarcopenia?

Sarcopenia is a term coined by Rosenberg in 1989, combining the Greek words "sarx," meaning muscle, and "penia," meaning loss (Rosenberg 1989). When this term was first proposed, it meant only a decrease in skeletal muscle mass, but since the European Working Group on Sarcopenia in Older People (EWGSOP) reported

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new diagnostic criteria in 2010 (Cruz-Jentoft et al. 2010), it has become common to define sarcopenia as a combination of skeletal muscle loss and muscle weakness/physical function decline. We organized the Asian Working Group (AWGS) for Sarcopenia in 2013 and proposed an algorithm specific for Asian people in 2014 (Chen et al. 2014). A new ICD-10-CM disease code for sarcopenia (M62.84) was established in October 2016, and many countries have accepted sarcopenia as a disease entity. Recently, the importance of muscle quality in addition to quantity and strength as skeletal muscle indicators has been indicated, and the understanding of sarcopenia is gradually changing with the progression of research.

12.2 How to Diagnose Sarcopenia

There are several international diagnostic criteria for sarcopenia, including the EWGSOP2 (Cruz-Jentoft et al. 2019), AWGS 2019 (Chen et al. 2020), International Working Group on Sarcopenia (IWGS) (Fielding et al. 2011), and the Foundation for the National Institutes of Health Sarcopenia Project (FNIH) (Studenski et al. 2014) criteria (Table 12.1). All of the criteria include measurements of skeletal muscle mass and physical function. However, muscle strength assessment is not included in the IWGS criteria.

In terms of appendicular skeletal muscle mass, the method of correcting muscle mass using the square of the height or body mass index (BMI) has been used. Although there is currently no consensus on which correction method is more appropriate (Cruz-Jentoft et al. 2019; Chen et al. 2020), we recently reported that low muscle mass with either height-squared or BMI correction was associated with adverse outcomes among Japanese older adults (Kinoshita et al. 2021b). The same study suggested that height-squared correction is more likely to miss sarcopenia associated with obesity, whereas BMI correction is more likely to miss sarcopenia associated with thinness (Kinoshita et al. 2021b). In addition, our study indicated that the cutoff value for low muscle mass with BMI correction in Asians may be lower than that the FNIH criterion (Moon et al. 2016; Kinoshita et al. 2021a), and the accumulation of evidence is necessary to establish an optimal cutoff value.

Table 12.1 Definitions of sarcopenia according to the different research groups

	Skeletal muscle mass	Physical function	Muscle strength
EWGSOP	○	○	○
AWGS	○	○	○
IWGS	○	○	
FNIH	○	○	○

EWGSOP European Working Group on Sarcopenia in Older People, *AWGS* Asian Working Group for Sarcopenia, *IWGS* International Working Group on Sarcopenia, *FNIH* Foundation for the National Institutes of Health Sarcopenia Project

Although physical function indicators are included in many criteria, they were positioned as outcome indicators in the FNIH criteria and as severity assessment indicators in the EWGSOP2 criteria. Walking speed is a typical physical function assessment, but the AWGS 2019 criteria also includes the five times sit-to-stand test and the Short Physical Performance Battery (SPPB) as physical function measures and proposes cutoff values based on evidence from Asian populations.

12.3 AWGS 2019

Here, we take the most recent criteria, the AWGS 2019 criteria, as an example and outline its contents. AWGS published a consensus report (AWGS 2019) (Chen et al. 2020), which was a revised version of the diagnostic criteria reported in 2014 (Chen et al. 2014). Since there are many older people with or at risk of sarcopenia in Asian countries with aging populations, the AWGS 2019 proposed the use of community or primary care settings in addition to clinical settings to diagnose sarcopenia (Fig. 12.1). The diagnostic indicators are muscle strength, physical function, and skeletal muscle mass, and sarcopenia is determined by low skeletal muscle mass plus low muscle strength or low physical function. The reference values for each of these are determined by data from representative cohort studies in Asian countries and by expert consensus (Table 12.2).

The flow of the AWGS 2019 guidelines in the clinical setting is described below. The process begins with the detection of patients with possible sarcopenia based on

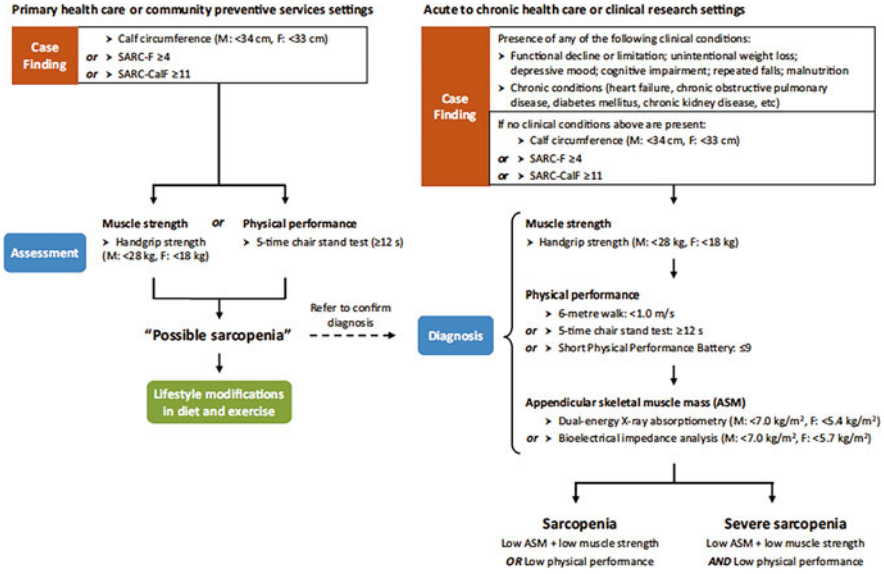

Fig. 12.1 Diagnostic algorithm of sarcopenia in AWGS 2019 (Chen et al. 2020)

Table 12.2 Cutoff values for diagnosing sarcopenia according to the AWGS 2019 criteria

	Men	Women
Calf circumference	<34 cm	<33 cm
SARC-F	≧4	
Grip strength	<28 kg	<18 kg
5 times sit-to-stand test	≧12 s	
Gait speed	<1.0 m/s	
Short Physical Performance Battery	≦9	
Skeletal muscle index		
Bioelectrical impedance	<7.0 kg/m^2	<7.0 kg/m^2
Dual-energy X-ray absorptiometry	<7.0 kg/m^2	<5.4 kg/m^2

clinical symptoms and case finding. The clinical symptoms include functional decline and weight loss, whereas case finding tests include calf circumference, SARC-F and SARC-CalF. This is followed by measurements of muscle strength (grip strength), physical function (gait speed, 5 times sit-to-stand test, and SPPB), and skeletal muscle mass (dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance (BIA)). Skeletal muscle mass loss is a requirement for diagnosing sarcopenia, and sarcopenia is determined when muscle weakness or physical function decline is observed. If all three indicators of skeletal muscle mass loss, muscle weakness, and physical function decline are present, the patient is judged to have severe sarcopenia. In community or primary care settings, grip strength and five times sit-to-stand tests should be performed for the diagnosis of possible sarcopenia after case finding with calf circumference measurements or SARC-F/SARC-CalF. Thus, the diagnosis of sarcopenia is widely applicable in almost all clinical settings based on the AWGS 2019 criteria.

12.4 Utilization of Phase Angle

In recent years, with the increase in the use of BIA to measure skeletal muscle mass, the phase angle (PhA), which is calculated from reactance and resistance measured by BIA, has become the focus of attention. PhA is thought to reflect the physiological functioning level of the cell, and in unhealthy cells, the reactance at the cell membrane is reduced, resulting in a lower PhA. It has been shown to be related to the quantity and quality of skeletal muscle, muscle strength, and physical function (Basile et al. 2014; Yamada et al. 2017, 2019) and has been reported to be useful in identifying sarcopenia (Di Vincenzo et al. 2021). Characteristically, PhA, like muscle strength, changes sensitively with training (Dos Santos et al. 2016) and is thought to be useful as an outcome measure for determining the effectiveness of interventions. Although PhA is not included in the diagnostic algorithm for sarcopenia, further evidence could support the inclusion of PhA as a criterion for sarcopenia.

12.5 Prevalence of Sarcopenia

The prevalence of sarcopenia varies widely by age, definition, and study setting. Reports that have determined age-specific prevalence rates in community-dwelling older adults have shown that the prevalence of sarcopenia increases with age, especially after the age of 75 years (Yamada et al. 2013; Kitamura et al. 2021). In addition, a systematic review examining the prevalence of sarcopenia in community-dwelling older adults using each diagnostic guideline reported a 12.9% prevalence by the EWGSOP criteria and AWGS criteria, a 9.9% prevalence by the IWGS criteria, and an 18.6% prevalence by the FNIH criteria (Mayhew et al. 2019). Furthermore, a systematic review examining the prevalence by setting showed that the prevalence was 11% in males and 9% in females among community-dwelling older people, 51% in males and 31% in females among nursing home residents, and 23% in males and 24% in females among inpatients (Papadopoulou et al. 2020). Thus, although the prevalence varies somewhat according to diagnostic criteria and setting, the high prevalence of sarcopenia is noteworthy and indicates the need for widespread measures.

12.6 Etiology of Sarcopenia

A variety of factors are thought to be associated with sarcopenia, including inactivity and poor nutrition, as well as few exercise units, chronic inflammation, increased oxidative stress, and increased insulin resistance (Fig. 12.2) (Dickinson et al. 2013). In this context, inactivity and poor nutrition are variable factors, and there is ample room for intervention.

12.7 Genetics of Sarcopenia

Although extensive studies on the genetic basis of muscle quality and quantity have been performed to date, there is insufficient evidence to demonstrate a causal relationship with sarcopenia, suggesting that the multifactorial mechanisms underpinning muscle regulation may not be reducible to one single gene or gene variant. Pratt et al. conducted a systematic review demonstrating that the alpha-actinin (*ACTN3*), angiotensin-converting enzyme (*ACE*), and vitamin D receptor (*VDR*) genotypes and ten DNA polymorphisms were significantly associated with muscle phenotypes (Pratt et al. 2019). Further studies need to be conducted to elucidate the causal relationship of specific genotypes or gene polymorphisms to predict the development of sarcopenia in humans. In addition, microRNAs are promising candidates for sarcopenia research because they are involved in the proliferation, differentiation, and stem cell renewal of skeletal muscle and the aging-related loss of

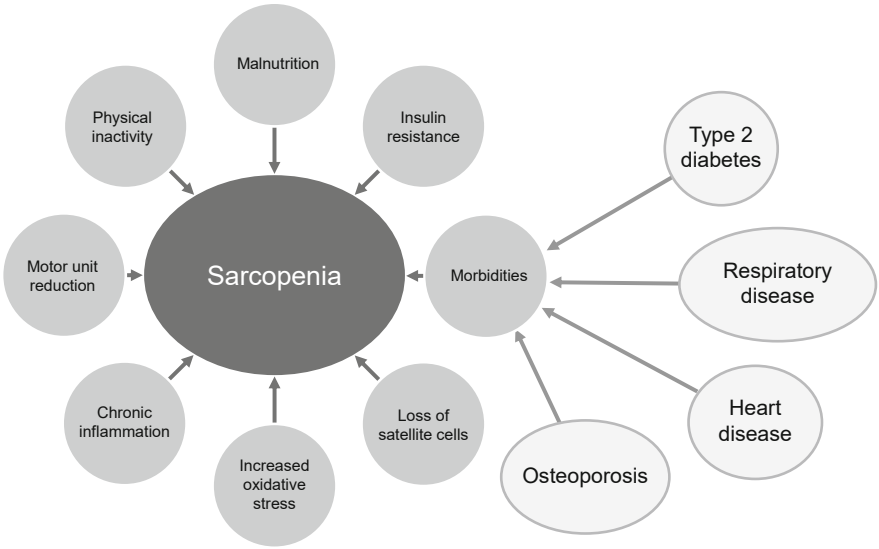

Fig. 12.2 Factors associated with sarcopenia

muscle mass (Jung et al. 2019). Jung et al. conducted a comprehensive review on the role of microRNAs in skeletal muscle aging and highlighted their potential as biomarkers or therapeutic targets (Jung et al. 2019).

12.8 Prognosis of Sarcopenia

Sarcopenia is known to be strongly associated with the development of subsequent adverse health outcomes, such as falls, fractures, hospitalization, disability, and death (Fig. 12.3) (Bianchi et al. 2016; Beaudart et al. 2017; Liu et al. 2017; Uemura et al. 2019; Yeung et al. 2019; Zhang et al. 2020; Huang et al. 2021). It is characterized not only by falls, fractures, and disability, which are directly affected by muscle weakness, but also by outcomes such as hospitalization and death.

12.9 Relationship Between Sarcopenia and Disease

Although sarcopenia is an age-related disease, many people with comorbidities are likely to develop sarcopenia. Among them, so-called secondary sarcopenia caused by diseases, such as type 2 diabetes, respiratory disease, cardiovascular disease, and osteoporosis, can develop (Fig. 12.3) (Pacifico et al. 2020). In particular, osteoporosis is strongly associated with sarcopenia; previous studies have shown that

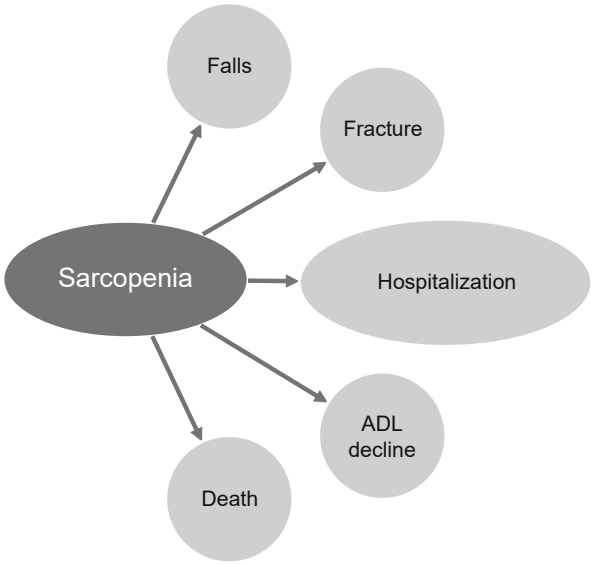

Fig. 12.3 Prognosis of sarcopenia

sarcopenia and osteoporosis often coexist (Huo et al. 2015; Drey et al. 2016), and the concept of osteosarcopenia has been proposed (Fagundes Belchior et al. 2020). Recently, the association between cognitive decline and sarcopenia has also been indicated (Chang et al. 2016), but since both are affected by aging, their interpretation needs careful consideration.

12.10 Macroscopic Features of Age-Related Changes in Skeletal Muscle

It is obvious that skeletal muscles undergo age-related changes. Various studies have shown that skeletal muscle mass shows a gradual decline among total body muscle mass starting at approximately 40–50 years of age (Fig. 12.4) (Speakman and Westerterp 2010; Jackson et al. 2012; Yamada et al. 2014), and in sarcopenic individuals, the amount of decline deviates from that associated with the normal aging process. However, such age-related changes do not occur in the same way in all skeletal muscles, of which there are more than 400 in the whole body; a study on age-related changes in muscle strength over a 10-year period showed that muscle weakness was more pronounced in the lower limbs than in the upper limbs in both men and women (Hughes et al. 2001). A study that included the trunk showed that so-called antigravity muscles were more likely to be affected (Fig. 12.5) (Vitasalo et al. 1984). In particular, among the anti-gravity muscles, relatively large muscle groups located near the body surface have a common characteristic of containing a large number of type 2 fibers and are prone to age-related changes. Among them, the

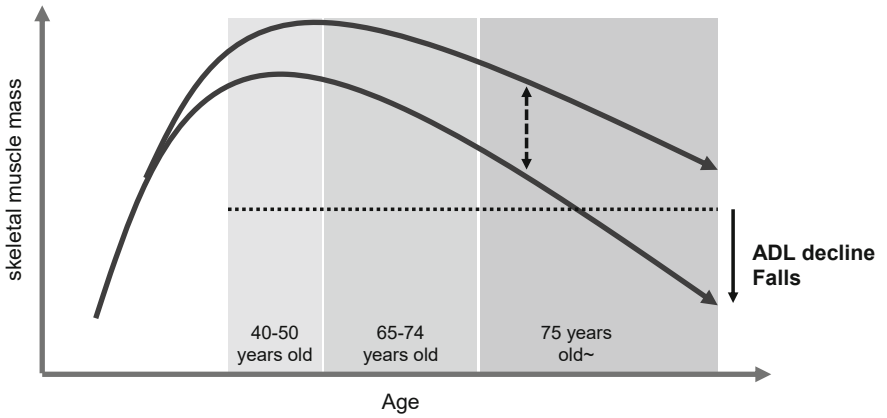

Fig. 12.4 Age-dependent changes in skeletal muscle

quadriceps, which is a representative anti-gravity muscle, is an especially major indicator of age-related changes in skeletal muscle. In our study, the quadriceps muscle showed greater age-related changes than the other muscles in the thigh region, and such changes were more pronounced in males than in females (Kasai et al. 2015). In a study using CT cross-sections in the same cohort, the quadriceps cross-sectional area was found to be associated with lower extremity muscle strength just as much as or more than the skeletal muscle mass index (SMI) obtained by DXA (Tsukasaki et al. 2020). Moreover, the muscle cross-sectional area, which represents muscle mass, as well as CT values, which represent muscle quality, were independently associated with muscle strength (Mizuno et al. 2021). Similarly, in a recent study in frailty-clinic outpatients assessed with CT cross-sectional images of the quadriceps muscle, muscle cross-sectional area was more closely related to muscle strength, whereas CT values were more closely related to physical function (Oba et al. 2021).

12.11 Microscopic Features of Age-Related Changes in Skeletal Muscle

Age-related changes in skeletal muscle naturally occur in the muscle fibers. Age-related changes in muscle fibers have two characteristics: (1) a decrease in the number of muscle fibers and (2) a decrease in the cross-sectional area of muscle fibers (Lexell 1995). The latter is a common feature of disuse muscular atrophy, while the former is a characteristic unique to age-related changes that are not observed in disuse muscular atrophy (Table 12.3) (Kanazawa et al. 2017). In addition, although muscle fibers can be broadly classified into type 1 fibers and type 2 fibers, it has been shown that type 2 fibers are more susceptible to the effects of aging, whereas type 1 fibers are relatively easy to maintain (Fig. 12.6) (Lexell

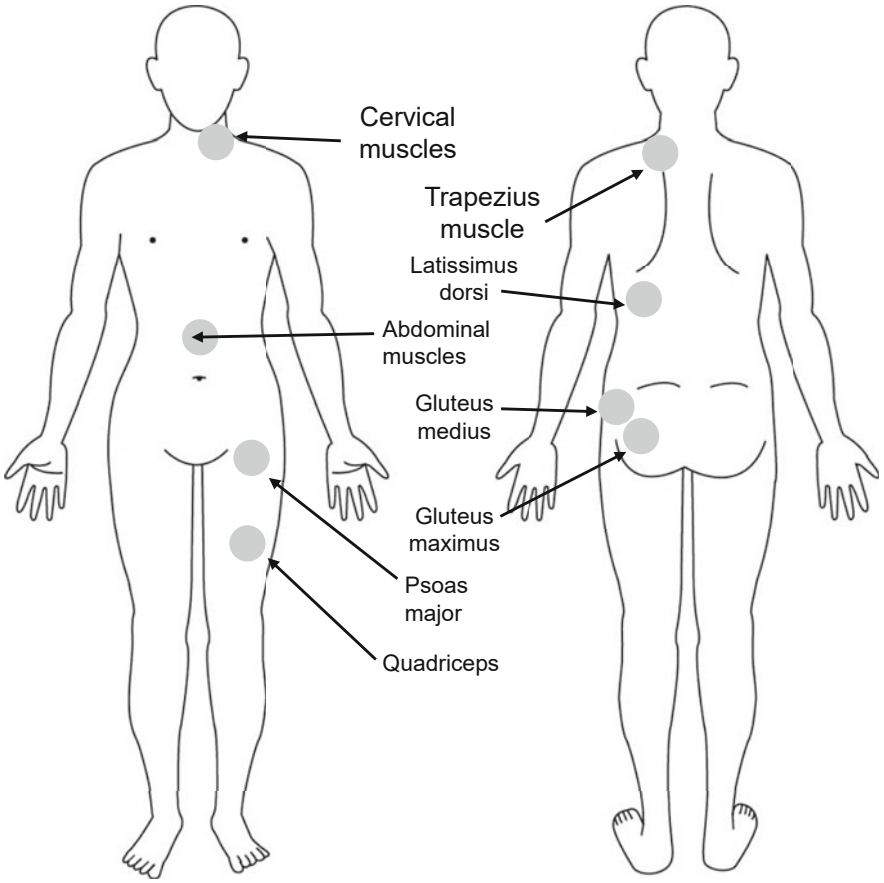

Fig. 12.5 Muscles that tend to be influenced by age

Table 12.3 Characteristics of sarcopenia caused by aging and disuse

	Age-related sarcopenia	Disuse-related sarcopenia
Number of muscle fibers	↓	→
Cross sectional area of muscle fibers	↓	↓

1995). One of the reasons for this difference is thought to be the influence of satellite cells. Satellite cells are considered to be involved in the repair and hypertrophy of myofibers, and it has been shown that satellite cells in type 2 fibers decrease with age, whereas satellite cells in type 1 fibers are unaffected (Verdijk et al. 2007). While changes in muscle fiber type are a factor pertaining to muscle quality, other micro changes related to muscle quality include increased accumulation of intra- and intermuscular fat (Goodpaster et al. 2001; Therkelsen et al. 2016), increased muscle fibrosis (Brack et al. 2007), and increased fat indicated by lower CT values on CT images (Aubrey et al. 2014).

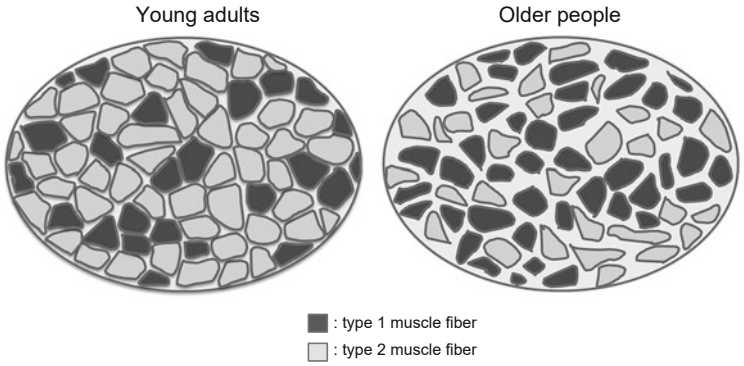

Fig. 12.6 Age-related changes in type 1 and 2 muscle fibers in human cells (image of cross-section of skeletal muscle on electron microscopy)

12.12 Prevention of Sarcopenia

There are few studies that consider the development of sarcopenia as an outcome, and it is not clear whether various interventions can prevent the development of sarcopenia. Several interventional studies have examined the effects of exercise and protein intake on skeletal muscle mass and strength; however, the outcomes were not limited to the occurrence of sarcopenia. A meta-analysis showed that resistance exercise increased muscle strength and skeletal muscle mass in healthy older people (Borde et al. 2015). On the other hand, a meta-analysis examining the effects of protein intake on muscle strength and skeletal muscle mass in healthy older subjects did not find any advantage of protein intake (Ten Haaf et al. 2018). In many cases, healthy older people are able to consume sufficient amounts of protein from their daily diet, and it is thought that the significance of additional protein is unlikely to affect outcomes.

12.13 Interventions for Sarcopenia

Exercise, protein (essential amino acids) intake, and a combination of these interventions have been shown to be effective for the treatment of sarcopenia. Resistance exercise has been shown to be effective for the treatment and prevention of sarcopenia and has been shown to improve skeletal muscle mass, muscle strength, and physical function (Yoshimura et al. 2017; Arai et al. 2018; Bao et al. 2020). In addition, it is known that protein intake, which is not significant in the prevention of sarcopenia, has a significant effect on skeletal muscle in sarcopenic subjects (Komar et al. 2015).

12.14 How to Provide Resistance Training

When resistance exercise is performed for the purpose of preventing or treating sarcopenia, the following two points should be carefully considered. The first is awareness of the number of repetitions as well as the amount of load, and the second is the continuation of exercise.

In general, when resistance exercise is performed for the purpose of muscle strengthening, it is considered ideal to perform it with a high load of 70–80% of the maximum performance. However, in recent years, it has been shown that muscle protein synthesis and muscle strengthening effects can be obtained by performing many repetitions with low loads rather than high loads when the target population is older people (Van Roie et al. 2013; Agergaard et al. 2017). This evidence is important when prescribing exercise for older adults with various risk levels, and the fact that increased repetitions, even at low loads, can help counteract sarcopenia is important information.

The effects of resistance exercise are not permanent and disappear in a relatively short period of time. Studies with a 12-week resistance exercise period followed by a 24-week rest period showed that muscle strength and muscle mass gained through resistance exercise were almost halved after 12 weeks and almost completely lost after 24 weeks (Fig. 12.7) (Taaffe et al. 2009; Zech et al. 2012; Yasuda et al. 2014). This trend was also observed for muscle quality, and it has been shown that muscle density and phase angle, which are indicators of muscle quality, improve with training and worsen with the cessation of training (Taaffe et al. 2009; Dos Santos

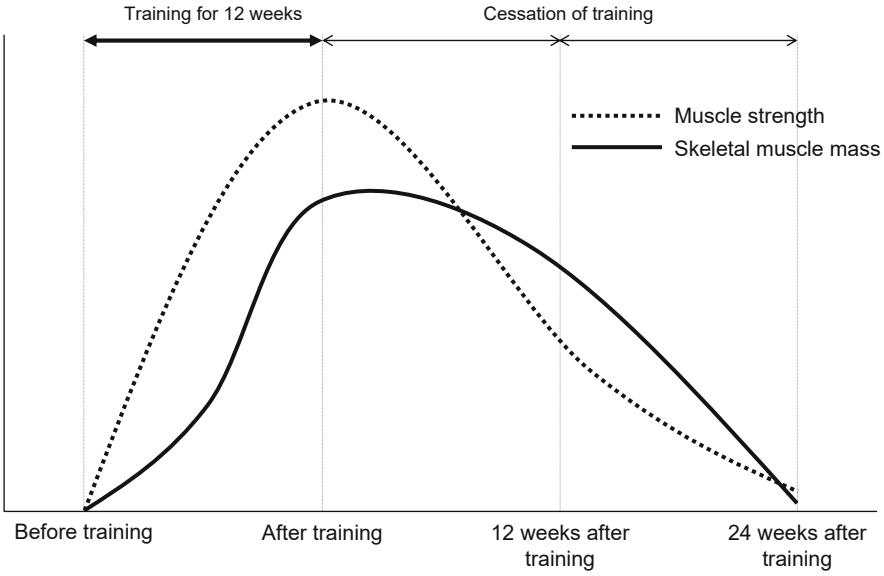

Fig. 12.7 Effects of resistance exercise on muscle strength and skeletal muscle mass

et al. 2016). Therefore, it is important for patients to continue exercise and to promote awareness of and behavioral changes focusing on low-load, high-repetition exercise as described above for a long period of time.

12.15 How to Provide Amino Acids and Protein for Persons with Sarcopenia

Although amino acid and protein intake have been demonstrated to be useful in the treatment of sarcopenia, the method of intake also needs to be examined. In general, amino acid/protein intake immediately after exercise is considered beneficial, but this method is not necessarily optimal for older subjects. It is known that muscle protein synthesis is accelerated 1–2 h after exercise in both young and older people in a similar manner (Kumar et al. 2009). However, when protein is ingested, more time is needed to increase the amino acid concentration in the blood, and it peaks after approximately 1 h in young people and 3 h in older people (Milan et al. 2015). In other words, protein intake immediately after exercise contributes to the promotion of postexercise muscle protein synthesis in young people, but it is difficult to contribute to the promotion of postexercise muscle protein synthesis in older people, even if protein is consumed immediately after exercise.

Against this background, in recent years, there has been a renewed emphasis on the need to maintain a balance between three daily meals. This is based on the idea that by maintaining a uniform protein intake in all three meals, the amino acid concentration in the blood will be maintained above a certain level throughout the day. In general, protein intake at breakfast tends to be inadequate and increases gradually with lunch and dinner (Paddon-Jones et al. 2015). Therefore, if protein is to be provided as a supplement, it is considered important to fortify protein in the morning. Muscle protein synthesis is more likely to decrease not only in the morning but also when protein intake is uneven among the three meals than when it is uniform (Paddon-Jones et al. 2015). Therefore, in the case of sarcopenia prevention, the current protein balance among the three meals should be examined, and the same daily protein intake should be maintained. In the case of treatment, the daily protein intake should be increased while maintaining a balance among the three meals.

12.16 Pharmacological Treatment of Sarcopenia

Although a variety of drugs for sarcopenia, including myostatin/ActR2 signaling inhibitors, exercise mimetics, anabolic hormones, and natural compounds, have been investigated for sarcopenia treatment, none have been approved for clinical use. For example, one novel approach targets the myostatin/activin type II receptor (ActRII) pathway to induce hypertrophy of skeletal muscles, with the expectation of

improved functional ability (Lach-Trifilieff et al. 2014). Bimagrumab (BYM338) is a fully human monoclonal antibody that can block ligand binding and promote the differentiation of human myoblasts (Rooks and Roubenoff 2019). However, no significant improvement in skeletal muscle function in old sarcopenic patients was shown in a preclinical study (Rooks et al. 2020). Further drug development for the treatment of sarcopenia is warranted because a significant number of sarcopenic patients cannot perform resistance training or achieve appropriate nutritional intake, as suggested by the recommendation.

12.17 Conclusions

Here, we summarized the current status of the concept, pathogenesis, diagnosis, and epidemiology of and intervention methods for sarcopenia. Sarcopenia is still a relatively new concept, and only recently has clinical research been actively pursued. Therefore, there are limits to what is known, and many unknowns remain in this field. We hope that an interdisciplinary approach to sarcopenia will contribute to global aging research by consolidating knowledge from around the world.

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Conflicts of Interest None.

References

Agergaard J, Bülow J, Jensen JK, Reitelseder S, Drummond MJ, Schjerling P, Scheike T, Serena A, Holm L (2017) Light-load resistance exercise increases muscle protein synthesis and hypertrophy signaling in elderly men. Am J Physiol Endocrinol Metab 312:E326–E338

Arai H, Wakabayashi H, Yoshimura Y, Yamada M, Kim H, Harada A (2018) Chapter 4 Treatment of sarcopenia. Geriatr Gerontol Int 18(Suppl 1):28–44

Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, Mazurak VC (2014) Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol 210:489–497

Bao W, Sun Y, Zhang T, Zou L, Wu X, Wang D, Chen Z (2020) Exercise programs for muscle mass, muscle strength and physical performance in older adults with sarcopenia: a systematic review and meta-analysis. Aging Dis 11:863–873

Basile C, Della-Morte D, Cacciatore F, Gargiulo G, Galizia G, Roselli M, Curcio F, Bonaduce D, Abete P (2014) Phase angle as bioelectrical marker to identify elderly patients at risk of sarcopenia. Exp Gerontol 58:43–46

Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O (2017) Health outcomes of sarcopenia: a systematic review and meta-analysis. PLoS One 12:e0169548

Bianchi L, Ferrucci L, Cherubini A, Maggio M, Bandinelli S, Savino E, Brombo G, Zuliani G, Guralnik JM, Landi F, Volpato S (2016) The predictive value of the EWGSOP definition of sarcopenia: results from the InCHIANTI study. J Gerontol A Biol Sci Med Sci 71:259–264

Borde R, Hortobágyi T, Granacher U (2015) Dose-response relationships of resistance training in healthy old adults: a systematic review and meta-analysis. Sports Med 45:1693–1720

Brack AS, Conboy MJ, Roy S, Lee M, Kuo CJ, Keller C, Rando TA (2007) Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science 317:807–810

Chang KV, Hsu TH, Wu WT, Huang KC, Han DS (2016) Association between sarcopenia and cognitive impairment: a systematic review and meta-analysis. J Am Med Dir Assoc 17:1164.e7–1164.e15

Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H (2014) Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 15:95–101

Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, Jang HC, Kang L, Kim M, Kim S, Kojima T, Kuzuya M, Lee JSW, Lee SY, Lee WJ, Lee Y, Liang CK, Lim JY, Lim WS, Peng LN, Sugimoto K, Tanaka T, Won CW, Yamada M, Zhang T, Akishita M, Arai H (2020) Asian Working Group for Sarcopenia: 2019 Consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc 21:300–307.e2

Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 39:412–423

Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M, Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2 (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48:16–31

Di Vincenzo O, Marra M, Di Gregorio A, Pasanisi F, Scalfi L (2021) Bioelectrical impedance analysis (BIA)-derived phase angle in sarcopenia: a systematic review. Clin Nutr 40:3052

Dickinson JM, Volpi E, Rasmussen BB (2013) Exercise and nutrition to target protein synthesis impairments in aging skeletal muscle. Exerc Sport Sci Rev 41:216–223

Dos Santos L, Cyrino ES, Antunes M, Santos DA, Sardinha LB (2016) Changes in phase angle and body composition induced by resistance training in older women. Eur J Clin Nutr 70:1408–1413

Drey M, Sieber CC, Bertsch T, Bauer JM, Schmidmaier R (2016) FiAT intervention group. Osteosarcopenia is more than sarcopenia and osteopenia alone. Aging Clin Exp Res 28:895–899

Fagundes Belchior G, Kirk B, Pereira da Silva EA, Duque G (2020) Osteosarcopenia: beyond age-related muscle and bone loss. Eur Geriatr Med 11:715–724

Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 12:249–256

Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB (2001) Attenuation of skeletal muscle and strength in the elderly: the health ABC study. J Appl Physiol 90:2157–2165

Huang P, Luo K, Xu J, Huang W, Yin W, Xiao M, Wang Y, Ding M, Huang X (2021) Sarcopenia as a risk factor for future hip fracture: a meta-analysis of prospective cohort studies. J Nutr Health Aging 25:183–188

Hughes VA, Frontera WR, Wood M, Evans WJ, Dallal GE, Roubenoff R, Fiatarone Singh MA (2001) Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. J Gerontol A Biol Sci Med Sci 56:B209–B217

Huo YR, Suriyaarachchi P, Gomez F, Curcio CL, Boersma D, Gunawardene P, Demontiero O, Duque G (2015) Comprehensive nutritional status in sarco-osteoporotic older fallers. J Nutr Health Aging 19:474–480

Jackson AS, Janssen I, Sui X, Church TS, Blair SN (2012) Longitudinal changes in body composition associated with healthy ageing: men, aged 20-96 years. Br J Nutr 107:1085–1091

Jung HJ, Lee KP, Kwon KS, Suh Y (2019) MicroRNAs in skeletal muscle aging: current issues and perspectives. J Gerontol A Biol Sci Med Sci 74:1008–1014

Kanazawa Y, Ikegami K, Sujino M, Koinuma S, Nagano M, Oi Y, Onishi T, Sugiyo S, Takeda I, Kaji H, Shigeyoshi Y (2017) Effects of aging on basement membrane of the soleus muscle during recovery following disuse atrophy in rats. Exp Gerontol 98:153–161

Kasai T, Ishiguro N, Matsui Y, Harada A, Takemura M, Yuki A, Kato Y, Otsuka R, Ando F, Shimokata H (2015) Sex- and age-related differences in mid-thigh composition and muscle quality determined by computed tomography in middle-aged and elderly Japanese. Geriatr Gerontol Int 15:700–706

Kinoshita K, Satake S, Matsui Y, Arai H (2021a) Quantifying muscle mass by adjusting for body mass index is the best for discriminating low strength and function in Japanese older outpatients. J Nutr Health Aging 25(4):501–506

Kinoshita K, Satake S, Matsui Y, Arai H (2021b) Association between sarcopenia and fall risk according to the muscle mass adjustment method in Japanese older outpatients. J Nutr Health Aging 25:762. https://doi.org/10.1007/s12603-021-1620-8

Kitamura A, Seino S, Abe T, Nofuji Y, Yokoyama Y, Amano H, Nishi M, Taniguchi Y, Narita M, Fujiwara Y, Shinkai S (2021) Sarcopenia: prevalence, associated factors, and the risk of mortality and disability in Japanese older adults. J Cachexia Sarcopenia Muscle 12:30–38

Komar B, Schwingshackl L, Hoffmann G (2015) Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. J Nutr Health Aging 19:437–446

Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, Williams J, Smith K, Seynnes O, Hiscock N, Rennie MJ (2009) Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. J Physiol 587: 211–217

Lach-Trifilieff E, Minetti GC, Sheppard K, Ibebunjo C, Feige JN, Hartmann S, Brachat S, Rivet H, Koelbing C, Morvan F, Hatakeyama S, Glass DJ. An antibody blocking activin type II receptors induces strong skeletal muscle hypertrophy and protects from atrophy. Mol Cell Biol 2014;34: 606-618

Lexell J (1995) Human aging, muscle mass, and fiber type composition. J Gerontol A Biol Sci Med Sci 50:11–16

Liu P, Hao Q, Hai S, Wang H, Cao L, Dong B (2017) Sarcopenia as a predictor of all-cause mortality among community-dwelling older people: a systematic review and meta-analysis. Maturitas 103:16–22

Mayhew AJ, Amog K, Phillips S, Parise G, McNicholas PD, de Souza RJ, Thabane L, Raina P (2019) The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. Age Ageing 48:48–56

Milan AM, D'Souza RF, Pundir S, Pileggi CA, Thorstensen EB, Barnett MP, Markworth JF, Cameron-Smith D, Mitchell CJ (2015) Older adults have delayed amino acid absorption after a high protein mixed breakfast meal. J Nutr Health Aging 19:839–845

Mizuno T, Matsui Y, Tomida M, Suzuki Y, Nishita Y, Tange C, Shimokata H, Imagama S, Otsuka R, Arai H (2021) Differences in the mass and quality of the quadriceps with age and sex and their relationships with knee extension strength. J Cachexia Sarcopenia Muscle 12:900

Moon JH, Kim KM, Kim JH, Moon JH, Choi SH, Lim S, Lim JY, Kim KW, Park KS, Jang HC (2016) Predictive values of the new sarcopenia index by the Foundation for the National Institutes of Health Sarcopenia Project for mortality among older Korean adults. PLoS One 11:e0166344

Oba H, Matsui Y, Arai H, Watanabe T, Iida H, Mizuno T, Yamashita S, Ishizuka S, Suzuki Y, Hiraiwa H, Imagama S (2021) Evaluation of muscle quality and quantity for the assessment of sarcopenia using mid-thigh computed tomography: a cohort study. BMC Geriatr 21:239

Pacifico J, Geerlings MAJ, Reijnierse EM, Phassouliotis C, Lim WK, Maier AB (2020) Prevalence of sarcopenia as a comorbid disease: a systematic review and meta-analysis. Exp Gerontol 131: 110801

Paddon-Jones D, Campbell WW, Jacques PF, Kritchevsky SB, Moore LL, Rodriguez NR, van Loon LJ (2015) Protein and healthy aging. Am J Clin Nutr 101:1339S–1345S

Papadopoulou SK, Tsintavis P, Potsaki P, Papandreou D (2020) Differences in the prevalence of sarcopenia in community-dwelling, nursing home and hospitalized individuals. A systematic review and meta-analysis. J Nutr Health Aging 24:83–90

Pratt J, Boreham C, Ennis S, Ryan AW, De Vito G (2019) Genetic associations with aging muscle: a systematic review. Cells 9:12

Rooks D, Roubenoff R. Development of pharmacotherapies for the treatment of Sarcopenia. J Frailty Aging 2019;8:120-130

Rooks D, Swan T, Goswami B, Filosa LA, Bunte O, Panchaud N, Coleman LA, Miller RR, Garcia Garayoa E, Praestgaard J, Perry RG, Recknor C, Fogarty CM, Arai H, Chen LK, Hashimoto J, Chung YS, Vissing J, Laurent D, Petricoul O, Hemsley S, Lach-Trifilieff E, Papanicolaou DA, Roubenoff R (2020) Bimagrumab vs optimized standard of care for treatment of sarcopenia in community-dwelling older adults: a randomized clinical trial. JAMA Netw Open 3:e2020836

Rosenberg I (1989) Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. Am J Clin Nutr 50:1231–1233

Speakman JR, Westerterp KR (2010) Associations between energy demands, physical activity, and body composition in adult humans between 18 and 96 y of age. Am J Clin Nutr 92:826–834

Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam TT, Vassileva MT (2014) The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 69:547–558

Taaffe DR, Henwood TR, Nalls MA, Walker DG, Lang TF, Harris TB (2009) Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. Gerontology 55:217–223

Ten Haaf DSM, Nuijten MAH, Maessen MFH, Horstman AMH, Eijsvogels TMH, Hopman MTE (2018) Effects of protein supplementation on lean body mass, muscle strength, and physical performance in nonfrail community-dwelling older adults: a systematic review and meta-analysis. Am J Clin Nutr 108:1043–1059

Therkelsen KE, Pedley A, Hoffmann U, Fox CS, Murabito JM (2016) Intramuscular fat and physical performance at the Framingham Heart Study. Age (Dordr) 38:31

Tsukasaki K, Matsui Y, Arai H, Harada A, Tomida M, Takemura M, Otsuka R, Ando F, Shimokata H (2020) Association of muscle strength and gait Speed with cross-sectional muscle area determined by mid-thigh computed tomography - a comparison with skeletal muscle mass measured by dual-energy X-ray absorptiometry. J Frailty Aging 9:82–89

Uemura K, Doi T, Lee S, Shimada H (2019) Sarcopenia and low serum albumin level synergistically increase the risk of incident disability in older adults. J Am Med Dir Assoc 20:90–93

Van Roie E, Delecluse C, Coudyzer W, Boonen S, Bautmans I (2013) Strength training at high versus low external resistance in older adults: effects on muscle volume, muscle strength, and force-velocity characteristics. Exp Gerontol 48:1351–1361

Verdijk LB, Koopman R, Schaart G, Meijer K, Savelberg HH, van Loon LJ (2007) Satellite cell content is specifically reduced in type II skeletal muscle fibers in the elderly. Am J Physiol Endocrinol Metab 292:E151–E157

Vitasalo JT, Era P, Vitasalo JT, Heikkinen E (1984) Muscular strength profiles and anthopometry in random samples of men aged 31–35, 51–55 and 71–75 years. Ergonomics 28:1563–1574

Yamada M, Nishiguchi S, Fukutani N, Tanigawa T, Yukutake T, Kayama H, Aoyama T, Arai H (2013) Prevalence of sarcopenia in community-dwelling Japanese older adults. J Am Med Dir Assoc 14:911–915

Yamada M, Moriguch Y, Mitani T, Aoyama T, Arai H (2014) Age-dependent changes in skeletal muscle mass and visceral fat area in Japanese adults from 40 to 79 years-of-age. Geriatr Gerontol Int 14(Suppl 1):8–14

Yamada Y, Buehring B, Krueger D, Anderson RM, Schoeller DA, Binkley N (2017) Electrical properties assessed by bioelectrical impedance spectroscopy as biomarkers of age-related loss of skeletal muscle quantity and quality. J Gerontol A Biol Sci Med Sci 72:1180–1186

Yamada M, Kimura Y, Ishiyama D, Nishio N, Otobe Y, Tanaka T, Ohji S, Koyama S, Sato A, Suzuki M, Ogawa H, Ichikawa T, Ito D, Arai H (2019) Phase angle is a useful indicator for muscle function in older adults. J Nutr Health Aging 23:251–255

Yasuda T, Fukumura K, Sato Y, Yamasoba T, Nakajima T (2014) Effects of detraining after blood flow-restricted low-intensity training on muscle size and strength in older adults. Aging Clin Exp Res 26:561–564

Yeung SSY, Reijnierse EM, Pham VK, Trappenburg MC, Lim WK, Meskers CGM, Maier AB (2019) Sarcopenia and its association with falls and fractures in older adults: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 10:485–500

Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H (2017) Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. J Am Med Dir Assoc 18:553.e1–553.e16

Zech A, Drey M, Freiberger E, Hentschke C, Bauer JM, Sieber CC, Pfeifer K (2012) Residual effects of muscle strength and muscle power training and detraining on physical function in community-dwelling prefrail older adults: a randomized controlled trial. BMC Geriatr 12:68

Zhang X, Huang P, Dou Q, Wang C, Zhang W, Yang Y, Wang J, Xie X, Zhou J, Zeng Y (2020) Falls among older adults with sarcopenia dwelling in nursing home or community: a meta-analysis. Clin Nutr 39:33–39