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REVIEW

Understanding of sarcopenia: from definition to therapeutic strategies

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Abstract Sarcopenia refers to the gradual loss of skeletal muscle mass and function along with aging and is a social burden due to growing healthcare cost associated with a super-aging society. Therefore, researchers have established guidelines and tests to diagnose sarcopenia. Several studies have been conducted actively to reveal the cause of sarcopenia and find an economic therapy to improve the quality of life in elderly individuals. Sarcopenia is caused by multiple factors such as reduced regenerative capacity, imbalance in protein turnover, alteration of fat and fibrotic composition in muscle, increased reactive oxygen species, dysfunction of mitochondria and increased inflammation. Based on these mechanisms, nonpharmacological and pharmacological strategies have been developed to prevent and treat sarcopenia. Although several studies are currently in progress, no treatment is available yet. This review presents the definition of sarcopenia and summarizes recent understanding on the detailed mechanisms, diagnostic criteria, and strategies for prevention and treatment.

Keywords Sarcopenia · Aging · Skeletal muscle · Satellite cell · Protein turnover

Introduction

While aging, a person faces attenuation of general physical and mental health. A person's organ functions decline, and often his/her cognitive functions may weaken. Due to advances in science and technology, the life expectancy of people has increased dramatically and aging has gained an immense attention sarcopenia (Cruz-Jentoft and Sayer 2019). In particular, a progressive muscle weakness during aging has gained extensive interest, and recently, researchers term this phenomenon as. Diverse approaches regarding the mechanism of sarcopenia and possible therapies have been studied vigorously in the last decade, and the Centers for Disease Control and Prevention (CDC) of the United States issued ICD-10-CM codes for sarcopenia in October 2016 (Falcon and Harris-Love 2017). Compared to other diseases that are frequently observed in the elderly, such as stroke, cancer and heart problems, sarcopenia has a relatively short history and people tend to think it as a much less lethal disease (Haehling et al. 2010). In this review, we aim to pay more attention to sarcopenia by introducing its newly established definition and diagnosis methods.

Definition

Sarcopenia is a term derived from the Greek phrase "poverty of flesh" (Rosenberg 1997). It was initially suggested in 1989 by Rosenberg (Rosenberg 1997). The concept for loss of muscle mass and function with age has since then been incorporated in the past decade (Dennison et al. 2017; Liguori et al. 2018). Sarcopenia is defined as a progressive and generalized skeletal muscle disorder accompanied by accelerated loss of muscle mass and function (Volpato et al. 2014). Recently, sarcopenia has been

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defined as a disease with numerous adverse effects, such as falls, functional decline, frailty and mortality (Cooper et al. 2012; Dennison et al. 2017).

Although approaches to define sarcopenia remain controversial and are still not fully accepted, several groups have proposed criteria for this condition (Dennison et al. 2017). The first and most widely cited definition is proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 (Cruz-Jentoft et al. 2010). Moreover, other working groups developed comparable definitions for sarcopenia. In 2018, EWGSOP2 updated the definition and diagnostic guidelines for sarcopenia, stating that a person with low muscle strength, muscle quantity/quality and physical performance will be diagnosed with sarcopenia (Cruz-Jentoft et al. 2019) (Table 1).

In order to precisely define sarcopenia, it is essential to understand the concept of geriatric syndromes such as frailty and cachexia. Frailty is a state of declined functions of multiple organ systems, resulting in difficulty to maintain homeostasis after stressor events (Gingrich et al. 2019) According to Fried's criteria, a phenotype of frailty is assessed by the presence of three or more of following components: unintentional weight loss, exhaustion, weakness, slowness and low physical activity level (Fried et al. 2001). Cachexia is defined as severe inflammation-associated weight loss and muscle wasting observed in various chronic illnesses such as cancer, AIDS, or end-stage organ failure (Doehner and Anker 2002; Peterson and Mozer 2017). According to Evans' criteria, cachexia is assessed by weight loss due to illness, accompanied by three or more of following components: decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormal biochemistry (Evans et al. 2008). Overlapping criteria have been noticed for defining sarcopenia, frailty and cachexia (Fig. 1). These three conditions are like deeply connected gear wheels, leading to adverse health outcomes.

Table 1 Sarcopenia: making a diagnosis

Stage	Muscle strength	Muscle quantity or quality	Physical performance
Sarcopenia probable	O	X	X
Sarcopenia confirmed	O	O	O
Sarcopenia severe	O	O	O

Age and Ageing 2019; 48: 16–31 Sarcopenia: revised European consensus on definition and diagnosis. https://doi.org/10.1093/ageing/afy169. Published electronically 24 September 2018

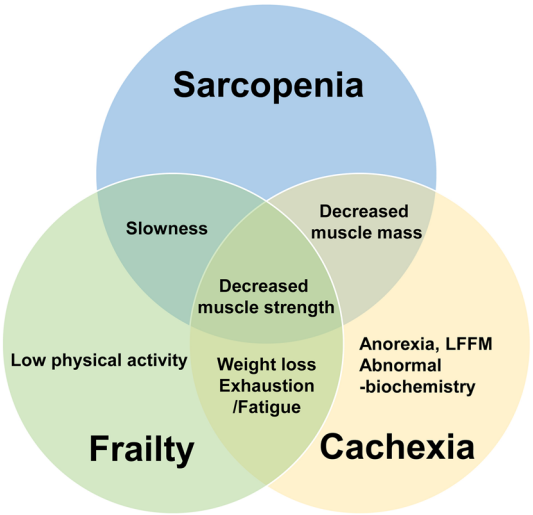

Fig. 1 Diagram of defining sarcopenia, frailty and cachexia. Frailty is a state of declined functions of multiple organ systems followed by unintentional weight loss, exhaustion, slowness and low physical activity. Cachexia is associated with decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormal biochemistry observed in cancer, AIDS, or end-stage organ failure. Overlapping criteria have been noticed for defining sarcopenia, frailty and cachexia

Epidemiology

A longitudinal study reveals that people aged 75 years lose muscle mass every year (at a rate of approximately 0.64–0.70% in women and 0.80–0.98% in men) and their muscle strength weakens at a rate of 3–4% every year in men and 2.5–3% in women (Mitchell et al. 2013). Because sarcopenia has not been initially considered as a disease, it has been difficult to estimate the number of people exposed to this condition; however, as the definition of sarcopenia is established, more cases are reported. Studies by using a definition by EWGSOP to collect statistics reports that 1.6% of European men and women aged 40–79 years presented sarcopenia (Gielen et al. 2015), and 3.6% of English men and women aged 85 years also had sarcopenia (Dodds et al. 2017).

Diagnosis

Diagnosis of sarcopenia depends on the measurement of muscle strength, muscle mass and physical performance (Cruz-Jentoft et al. 2010). These concepts also have used in defining sarcopenia; however, the exact standard of sarcopenia and evaluation method of these factors are not yet established. EWGSOP classified sarcopenia into three stages depending on its severity: pre-sarcopenia, sarcopenia and severe sarcopenia. Pre-sarcopenia is a stage in which muscle

mass decrease but muscle strength and physical performance are in the normal range. In sarcopenia, muscle mass and either the muscle strength or physical performance are lower than that in the previous stage. Lastly, if all factors associated with muscles are remarkably lower than the sarcopenia stage, then it is considered as the severe sarcopenia stage. The classification by EWGSOP and AWGS (Asian Working Group for Sarcopenia) helps clinicians in determining the right approach to treat sarcopenia (Chen et al. 2014; Cruz-Jentoft et al. 2019).

To measure muscle strength, the most frequent method used is grip strength testing, which is well-established compared to the other methods because of its convenience and low cost (Roberts et al. 2011). This test is usually conducted by dynamometer, a device for assessing grip strength (Richards et al. 1996; Guerra and Amaral 2009; Hogrel 2015). In recent years, studies have been revealed the correlation between isometric force of forearms (including hands) and entire body strength (Wind et al. 2010; Cruz-Jentoft et al. 2019). In this regard, EWGSOP2 adopted grip strength test as one of standard of assessing sarcopenia (Cruz-Jentoft et al. 2019). However, underlying conditions such as hand osteoarthritis, neurological disorders, and others can also cause weakening of a hand grip; hence, conducting differential diagnosis before the physician's intervention is recommended (Cruz-Jentoft and Sayer 2019). Although hand grip test can be used to speculate total muscle strength, there is a question of whether it reflects the muscle strength of the lower body (Steffl and Stastny 2020). In this regard, isokinetic testing which is used to measure the strength of knee muscles and hamstrings, has also been used to diagnose sarcopenia (Feiring et al. 1990; Hartmann et al. 2009; Duarte et al. 2018). Normally, isokinetic strength test is performed with constant angular velocity but variable resistance (Hartmann et al. 2009; Duarte et al. 2018; Osawa et al. 2018). Advantages of this test are accuracy, safety and repeatability. However, unlike grip test, this method is less accessible because of the diversity of analysis and high cost (Alonso et al. 2018).

Common methods to test muscle mass include dual X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), computerized tomography (CT) and magnetic resonance imaging (MRI) (Buckinx et al. 2018). DXA measures the lean mass, and BIA is preferred as it is a bedside test; however, the cutoff points differ among other machines and no criteria has been established for diagnosis (Gonzalez et al. 2018). MRI and CT are the most accurate imaging methods for measuring muscle mass. These methods reveal the density of muscle and infiltration of fat, which makes some people consider them as gold standards (Goodpaster et al. 2000). Recently, muscle ultrasound (M-US) is used for screening and diagnosis of sarcopenia, although the algorithm is not applicable for clinical usage (Ticinesi et al. 2017). All these methods are useful to diagnose sarcopenia but also have limitations such as unclear cutoff points and lack of correlation between measured muscle mass and adverse health outcomes. These factors make it difficult to standardize the method for muscle mass measurement (Manini and Clark 2012).

Physical performance can represent a person's physical ability to manage daily life independently (Cruz-Jentoft and Sayer 2019). Good physical performance indicates healthy organs and a healthy body, as well as a balance between the skeletal muscle, peripheral neuronal system and central nervous system. Single-objective evaluation such as measurement of gait speed and 400 m timed walk, and more complex methods such as Short Physical Performance Battery, Timed Up and Go tests, and the chair stand test (5 times sit to stand) can be used to test physical performance (Bischoff et al. 2003; Pavasini et al. 2016). EWGSOP2 states physical performance as a criterion for severity of sarcopenia (Cruz-Jentoft et al. 2019), and other specialists recommend physical performance to be applied while assessing the effect of sarcopenia treatment (Studenski et al. 2014), or to be included as one of the definitions of sarcopenia (Morley et al. 2011) (Table 2).

Biological mechanisms of sarcopenia

Sarcopenia is a complex geriatric syndrome caused by multifactorial conditions. Though the underlying mechanisms of sarcopenia remain unclear, several age-related factors contribute to the structural and functional exacerbation of skeletal muscle leading to sarcopenia (Fig. 2).

Dysfunction of satellite cell

Satellite cells are bona-fide muscle stem cells that can self-renew and differentiate into myoblasts, which can fuse to generate multi-nucleated myofibers. Satellite cells are distinct from other cells resident in muscles via expression of the transcription factor Pax3/Pax7 (paired box protein 3/paired box protein 7), which is critical for the maintenance and activation of satellite cells (Bentzinger et al. 2012; Almada and Wagers 2016). $Pax3^+$ and $Pax3^+/Pax7^+$ progenitor cells are specified to be muscle lineage-committed myoblasts. $Pax3^+$ cells generate embryonic muscle and $Pax7^+$ cells, and ablation of $Pax3^+$ cells result in failure of embryonic muscle formation (Kang and Krauss 2010). In the uninjured state, a satellite cell is in a nondividing stage, commonly defined as the quiescence. In $Pax7^+$ quiescent satellite cells, myogenic gens such as MYF5 and MYOD are repressed (Seale et al. 2000). In contrast, during muscle trauma, they are activated and proliferate expressing MYOD, a myogenic determination transcription factor revealing its

Table 2 Diagnosis of sarcopenia: measurable variables and cut-off points

Measure	Method	EWSOP	AWGS
Muscle strength	Grip test	Men: < 30 kg Women: < 20 kg	Men: < 27 kg Women: < 16 kg
Muscle mass	DXA	Men: 7.23–7.26 kg/m^2 Women: 5.5–5.67 kg/m^2	Men: < 7.0 kg/m^2 Women: < 5.4 kg/m^2
	BIA	Men: Severe sarcopenia ≤ 8.50 kg/m^2 Moderate sarcopenia 8.51–10.75 kg/m^2 Women: Severe sarcopenia ≤ 5.75 kg/m^2 Moderate sarcopenia 5.76–6.75 kg/m^2	Men: < 7.0 kg/m^2 Women: < 5.7 kg/m^2
Performance	SPPB	≤ 8 point score	≤ 9 point score
	Chair stand test (5times sit to stand)	> 15 s for 5 rises	> 12 s for 5 rises
	Walking test	400 m walk: Non-completion or ≥ 6 min for completion	6 m walk: < 1 m/s

Age and Ageing 2010; 39: 412–423 Sarcopenia: European consensus on definition and diagnosis. https://doi.org/10.1093/ageing/afq034. Published electronically 13 April 2010

Age and Ageing 2019; 48: 16–31 Sarcopenia: revised European consensus on definition and diagnosis. 10.1093/ageing/afy169. Published electronically 24 September 2018

Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment Liang-Kung Chen, Published: February 04, 2020. https://doi.org/10.1016/j.jamda.2019.12.012

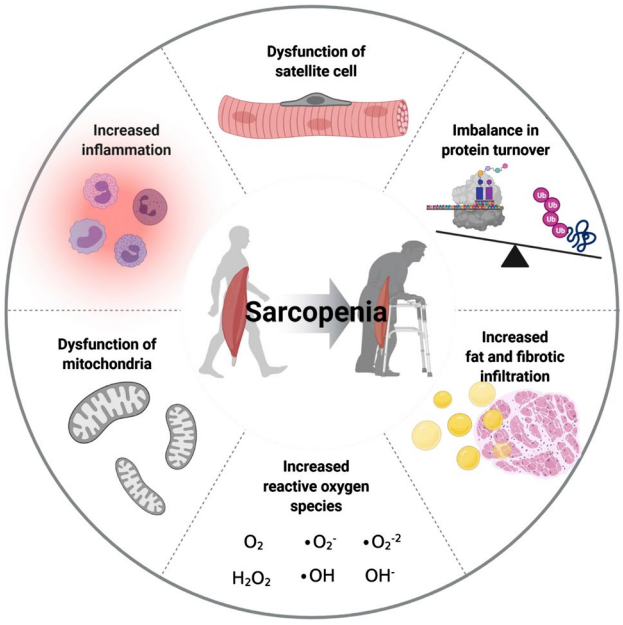

Fig. 2 Age-related factors causing sarcopenia. Decreased self-renewal and differentiating capacity of satellite cells cause impaired muscle regeneration. Increased protein degradation and decreased protein synthesis lead reduced muscle mass. Fatty and fibrotic accumulation cause poor muscle quality. Increased ROS induces oxidative stress leading muscle loss and strength. Associated with excessive ROS, dysfunction of mitochondria causes reduced ATP production. Lastly, elevated inflammation also induces oxidative stress and anabolic resistance leading loss of muscle. Created with BioRender.com

ability to act as a master regulator in driving tissue-specific transcription and cell differentiation (Almada and Wagers 2016). Subsequently, a subset of PAX7$^+$, MYOD$^+$ activated satellite cells differentiates into myoblasts to repair the injured muscle tissue, expressing MYOG (Almada and Wagers 2016). The other subset of activated satellite cells self-renews to replenish their pool by inhibiting MYOD (Bentzinger et al. 2012; Almada and Wagers 2016).

Satellite cells themselves decline in function over time. In aging, the total growth rate of myogenic cells does not match with the rate of reduction of functional muscle cells. Eventually, this results in a decrease in total number of muscle cells, which directly contributes to the loss of muscle mass. This phenomenon inevitably arises in aged individuals. One reason for this is the change in the character of satellite cells. In this section, we discuss the changes in satellite cells associated with sarcopenia, muscular atrophy and aging.

Changes in chromatin status associated with sarcopenia

Adult stem cells such as satellite cells retain their stemness and have the potential to differentiate through tight epigenetic regulations (Avgustinova and Benitah 2016). On quiescent satellite cells, the regulatory regions of cell cycle inhibitor p21 gene have high levels of H3R8me2 (Zhang et al. 2015). Also, a myogenic gene MYOD is silenced with high levels of H4K20me2 and H3K9me2 (Ling et al. 2012; Boonsanay et al. 2016). After the activation of satellite cells, DNA methylations of the myogenic transcription factors such as MYF5 and MYOD are reduced driving

differentiating program (Avgustinova and Benitah 2016). Likewise histone methylation, histone acetylation also regulates transcription of myogenic genes (Walsh and Van Remmen 2016). Increased H4K16Ac at MYOD leads myogenic differentiation (Ryall et al. 2015).

However, histone modification and chromatic landscape are changed during aging and this changes influence the gene expressions and genomic stability (Liu et al. 2013). A previous study reports that satellite cells from aged mice present increased levels of H3K27me3, a histone marker associated with heterochromatin (Liu et al. 2013). It is occurred globally throughout the genome especially in the transcription start site and intergenic regions of genes (Liu et al. 2013). Also, numerous studies reported elevated HDACs in aged muscle (Walsh et al. 2015; Walsh and Van Remmen 2016; Pigna et al. 2018). In this regard, HDACs could be potential targets for intervening sarcopenia through inhibiting them (Beharry et al. 2014; Walsh and Van Remmen 2016).

p38α/β MAPK

MAPK activation is associated with the differentiation capacity of various stem cell types. In particular, the p38MAPK (p38) pathway primarily controls satellite cell fate decisions (Keren et al. 2006). Indeed, several studies have demonstrated the important function of p38 pathway in the myogenic stage, where it acts to induce cell cycle withdrawal and expression of muscle-specific genes (Keren et al. 2006; Takaesu et al. 2006; Bae et al. 2009; Cruz-Jentoft et al. 2010; Jeong et al. 2020). p38 pathway must be strictly controlled because its hyperactivity inhibits asymmetric division, which is important for maintaining the pool of self-renewing satellite cells and differentiating myoblasts (Keren et al. 2006; Jeong et al. 2020).

Compared to young satellite cells, p38 signaling is highly activated in aged satellite cells leading to disruption of asymmetric division. Consequently, self-renewal satellite cells are reduced and differentiation of myoblasts is inhibited (Bernet et al. 2014; Blau et al. 2015). Furthermore, multiple studies have reported that p16Ink4a, a senescence marker, is activated by p38 during aging (Munoz-Espin and Serrano 2014; Zhu et al. 2019). It leads to breaking muscle homeostasis and impaired muscle regeneration by decreasing the self-renewal capacity of satellite cells (Bernet et al. 2014; Cosgrove et al. 2014; Almada and Wagers 2016).

Fibroblast growth factors (FGFs)

Numerous studies have reported that FGFs are essential for the self-renewal of satellite cells, muscle maintenance and the repair of muscle in the muscle trauma state (Kastner et al. 2000; Syverud et al. 2016; Pawlikowski et al. 2017; Xie et al. 2020). They trigger a number of intracellular pathways including p38, ERK, PI3K and AKT signalings. Of the 18 paracrine FGFs, FGF2 and FGF6 are main factors in regulating satellite cells (Pawlikowski et al. 2017). FGF2, considered as a mitogen, triggers proliferation of satellite cells. The role of FGF6 is controversial, but it has different functions in dose-dependent manner; promoting proliferation of the myogenic cells at high concentration, while regulating differentiation at low concentration.

In aged muscle, the expression of FGF2 is upregulated (Chakkalakal et al. 2012; Bernet et al. 2014). This phenomenon is not fully understood, but may due to the compensation to reduced FGF2 responsiveness in aged muscle (Shefer et al. 2006; Bernet et al. 2014; Li et al. 2015). Along with increased FGF2, elevated p38 pathway promotes differentiation and reduces self-renewal of satellite cells (Bernet et al. 2014; Cosgrove et al. 2014). Also with negative feedback, the expression of FGF inhibitor Sprouty 1 (Spry1) is downregulated resulting loss of quiescence of satellite cells (Chakkalakal et al. 2012).

Imbalance in protein turnover

Muscle mass is determined by the balance between protein synthesis and degradation (Liguori et al. 2018). With age, the balance between muscle protein anabolic and catabolic pathways is impaired, which indicates dysregulated proteostasis of muscle, leading to loss of muscle mass.

Protein synthesis

By hormones [such as insulin-like growth factor-1 (IGF-1) and insulin], nutrients (such as amino acids) and exercise, protein synthesis pathway is activated. A key molecule related to the anabolic pathway is mammalian target of rapamycin (mTOR). Upon binding of IGF-1 or insulin to IGF receptor, the receptor phosphorylated, leading to the sequential activation of phosphoinositide 3 kinase (PI3K) and Akt/PKB. Activated Akt/PKB promotes mTOR activation to inhibit the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and activate p70S6 kinase (p70S6K), leading to protein synthesis. Moreover, activated Akt/PKB suppresses protein degradation in muscle via phosphorylation of forkhead box 1 (FoxO1) transcription factors, thereby inhibiting the expression of the E3 ubiquitin ligases, such as atrogin-1 and muscle RING-finger protein-1 (MuRF-1) (Sandri et al. 2004). Amino acid signaling plays a very important role in protein synthesis. For example, the general-control nonderepressible (GCN2), which phosphorylates eIF2α and inhibits eIF2B activity, is activated in response to essential amino acid deficiency (Dever and Hinnebusch 2005). And nutrients, especially the branched amino acids (BCAAs), also promote protein synthesis

pathway in muscle through the activation of mTOR directly (Sartori et al. 2021).

Studies on basal levels of protein synthesis between young and old people have revealed conflicting results; however, some studies, focusing on postprandial state protein synthesis, implying the efficiency of utilizing proteins, revealed that older people have anabolic resistance (Haran et al. 2012). They have a blunted protein synthesis response to nutrients and exercise with decreased mTOR activation (Wang and Proud 2006). Although anabolic resistance presumably contributes to the onset of sarcopenia, it is unlikely that it may contribute to the continuous decrement in muscle mass (McCormick and Vasilaki 2018).

Protein degradation and quality control

The proteasomal degradation pathway and autophagy play a crucial role in maintaining the quality control of proteins (Pohl and Dikic 2019). The ubiquitin–proteasome system (UPS) regulates protein degradation. When transforming growth factor β (TGFβ) and myostatin bind to their receptors, Smad2/3 and TAK1/p38 are activated and induce the expression of atrogin-1 and MuRF-1 (Philip et al. 2005). As muscle specific E3 ubiquitin ligases, they polyubiquitinate target proteins, thereby inducing protein destruction by the proteasome system (Philip et al. 2005; Kimura et al. 2009; Elkina et al. 2011). Moreover, Smad2/3 can inhibit the PI3K/Akt signaling pathway and reduce the activation of p70S6K (Trendelenburg et al. 2009).

Studies evaluating age-related changes in protein-degradation pathways have revealed increased serum levels of TGFβ and intramuscular levels of myostatin in humans (Gumucio and Mendias 2013; Schiaffino et al. 2013). Although there are contradictory results on the expression of the E3 ubiquitin ligases atrogin-1 and MuRF-1 (Whitman et al. 2005), these results suggest that the UPS presumably contributes to sarcopenia in humans.

Autophagy is another mechanism responsible for the quality control of proteins (Arias and Cuervo 2011). It is a self-destructive process that removes unnecessary or dysfunctional components. This process is mainly controlled by Atg proteins and comprises three steps: initiation, nucleation and lysosome fusion/degradation (Nakatogawa et al. 2009). Autophagy in muscle is mainly induced by lack of nutrients and hormones (Kim et al. 2011). During fasting, Akt is inactivated, whereas AMP-activated protein kinase (AMPK) is activated, leading to the activation of FoxO3 and inactivation of mTOR. Activated FoxO3 induces the expression of Atg proteins and E3 ubiquitin ligases atrogin-1 and MuRF-1. And, inactivated mTOR allows the Unc-51 like autophagy activating kinase 1 (ULK1) complex to initiate nucleation (Neel et al. 2013). Appropriate regulation of muscle autophagy is crucial to maintain the muscle mass and function (Masiero and Sandri 2010). An imbalance of autophagy in muscle can cause loss of muscle mass. Excessive autophagy causes a quick loss in the muscle mass; however, insufficient autophagy leads to a chronic loss in muscle mass due to the buildup of damaged or aged cellular components (Sandri 2010).

Some studies have reported that the amount of certain autophagy-linked molecules is increased in the sarcopenic muscle of mice (Rong et al. 2020); however, other studies have reported reduced autophagy and increased accumulation of protein aggregates during aging (McCormick and Vasilaki 2018). Although conflicting results are observed regarding autophagic changes occurring within the aged muscle, these results provide evidence that autophagic dysregulation is associated with sarcopenia.

Increased fat and fibrotic infiltration

Fatty infiltration of muscle called myosteatosis, and accumulation of fibrous connective tissue in muscle are related to sarcopenia (Hamrick et al. 2016). Both fat and fibrotic infiltration of muscle increases with age and is associated with poor muscle quality. These factors are strongly related to metabolic abnormalities, poor strength and performance, and incident mobility disability. Moreover, it has been found that the degree of thigh intermuscular fat is significantly associated with higher levels of inflammatory markers (Hamrick et al. 2016).

Several mechanisms explain the fatty and fibrotic accumulation in muscles with different pathways based on their cellular origins with age (Hamrick et al. 2016). Muscle fibers are surrounded by adult muscle stem cells, namely satellite cells and fibroadipogenic progenitors (FAPs). During aging, satellite cells switch from a myogenic to an adipogenic or fibrotic fate. This change provides evidence suggesting that satellite cells are a possible source of intramuscular fat and fibrotic accumulation (McCormick and Vasilaki 2018). Another pathway for fat or fibrotic accumulation in muscles is intermuscular infiltration by FAPs. FAPs can differentiate into adipocytes or fibroblasts under muscle injury or glucocorticoid treatment (Joe et al. 2010; Dong et al. 2014). With age, increased Wnt signaling and chronic inflammatory responses stimulate the differentiation of FAPs into adipocytes or fibroblasts, leading to sarcopenia (Cisternas et al. 2014; McCormick and Vasilaki 2018).

Increased reactive oxygen species (ROS)

Reactive oxygen species (ROS) are considered crucial factors in controlling cell signaling and metabolism. They are eliminated by the antioxidant defense system, which is a part of the mitochondrial functions (Miquel et al. 1980). During aging, basal levels of ROS are increased in muscles

and satellite cells (Minet and Gaster 2012; Palomero et al. 2013). Increased ROS levels cause increased protein carbonylation; oxidation of lipids, DNA, and proteins; breakdown of myogenic proteins and damaged autophagy process; and inhibition of muscle cell differentiation (Mecocci et al. 1999; Scherz-Shouval et al. 2007; Sandiford et al. 2014; Sakellariou et al. 2016). Accumulated ROS with aging also induce apoptotic signaling cascades (Meng and Yu 2010; Barbieri and Sestili 2012). Activation of mitochondrial caspase-independent apoptosis, caspase 2- and JNK-mediated apoptosis causing age-related muscle loss are reported (Braga et al. 2008; Marzetti et al. 2008). Interestingly, ROS are responsible for neuro-muscular junction (NMJ) dysfunction in sarcopenia. The greater ROS production is reported in the NMJ region in older mice, which is associated with declined neurotransmitter release (Ivannikov and Van Remmen 2015). This likely lead to disturbance in action potential generation and decreased muscle strength related to sarcopenia.

Dysfunction of mitochondria

While mitochondria play a critical role in degrading ROS in muscles, they also function in ATP supply for muscle contraction and general cell survival. During aging, mitochondria dysfunction seems to be associated with increased ROS production, which results in mutations of mitochondrial DNA (Miquel et al. 1980). Mitochondrial dysfunction leads to impairment of the electron transport chain, causing increased production of ROS as well as reduced cellular ATP production (Miquel et al. 1980; Singh et al. 2021). Several studies have reported that increased ROS levels, mtDNA impairment, and mitochondrial dysfunction are associated with muscle atrophy in rodents and humans (Wanagat et al. 2001; Bua et al. 2006). These data suggest that mitochondrial dysfunction is responsible for sarcopenia. Furthermore, mitochondria in the muscle of sarcopenia patients reveals increased fusion and decreased fission, impairment of mitochondrial autophagy and proteasomal machinery (Yoon et al. 2006; Marzetti et al. 2008; Gouspillou et al. 2014).

Increased inflammation

Low levels of chronic inflammation are associated with a decline in the function of immune system in elderly, and this phenomenon is called "inflamm-aging" (Franceschi et al. 2000). As oxidative stress that becomes chronic in aging process induces inflammatory state and reinduces oxidative stress, the term "oxi-inflamm-aging" is introduced (Fuente and Miquel 2009; Liguori et al. 2018);. Increased serum levels of well-known inflammatory markers such as TNF-α, IL-1, IL-6 and C-reactive protein (CRP) are suggested to be correlated with decreased muscle mass, reduced muscle performance, diminished muscle function and weakened muscle strength (Pedersen et al. 2003; Thalacker-Mercer et al. 2010; Tiainen et al. 2010; Kim and Choi 2013; Bian et al. 2017; Dobbeleer et al. 2019). This condition is similar in patients with sarcopenia (Kim and Kim 2020). Interestingly, TNF-α, IL-6 and CRP can also have positive effects on skeletal muscle growth (McCormick and Vasilaki 2018). Therefore, it is proposed that this systemic inflammation during aging causes changes in the muscle mass and functions only when the inflammation rate exceeds a certain threshold or the period is long enough to trigger sarcopenia (McPhee et al. 2016).

Furthermore, inflammation causes anabolic resistance which can lead to sarcopenia (Chung et al. 2009). Anabolic resistance is a state in which a body cannot proceed with protein synthesis, in spite of the presence of sufficient amounts of amino acids and insulin by food intake (Dardevet et al. 2000; Prod'homme et al. 2004). Inflammation activates the ubiquitin–proteasome system by inhibiting the actions of IGF-1, thereby inducing anabolic resistance (Ogawa et al. 2016). When low-grade inflammation is eased, the muscle anabolism after a meal is restored in rats (Rieu et al. 2009). Also, CRP regulates catabolism of muscle through inhibiting AKT/PI3K and upregulating AMPK, which inhibits mTORC1 leading increased intracellular energy stress (Wahlin-Larsson et al. 2017).

Treatment: pharmacotherapy

Undoubtedly, exercise is essential for muscle maintenance and regeneration, and these facts have been reported in previous studies (Vinel et al. 2018); however, exercise can be difficult for certain elderly people and some patients. Therefore, different approaches are required to treat these individuals. Pharmacotherapy is one of these approaches with several targets, which may include hormonal manipulation or inhibitor of sarcopenia-associated factors such as myostatin.

Hormonal manipulation with androgen receptor

Hormonal manipulation is one of the well-known strategies to relieve sarcopenia (Dennison et al. 2017; Kwak and Kwon 2019). The key concept is the activation of androgen receptor to promote myogenesis and protein synthesis. Testosterone and selective androgen receptor modulation (SARM) can activate the androgen receptor and they are regarded promising candidates for the treatment of sarcopenia (Atkinson et al. 2010; Dalton et al. 2011).

Androgen receptors (ARs) are shown to be expressed in satellite cells and myoblasts. As one of ligands of ARs, testosterone can promote the entry of satellite cells into cell cycle, which increases the population of satellite cells (Sinha-Hikim et al. 2002). Other studies report that

testosterone increases the response of fusion-impaired myoblasts and improves the levels of ARs and AKT abundance (Kamel et al. 2002; Hughes et al. 2016; Pal et al. 2019). Another study reports that testosterone improves the efficiency of amino acid reutilization from protein breakdown (Ferrando et al. 1998).

SARMs are a novel class of androgen receptor ligands. They have same effects as androgen but can target specific tissues by optimizing characteristics. Several steroidal and nonsteroidal SARMs (Embosarm, MK-0773) have been conducted in clinical or preclinical trials (Dalton et al. 2011); however, the drug has yet been approved by the FDA due to hepatotoxicity and the unpredictable post-dose prognosis. Therefore, the drug is not practically used to date.

Inhibitor of sarcopenia-associated factors

Myostatin is a secretory factor that belongs to the TGF-β superfamily. It is mostly expressed in skeletal muscle and causes muscle wasting with other related factors such as atrogin-1 and MuRF-1. Numerous studies have demonstrated that myostatin attenuates satellite cell proliferation and inhibits muscle differentiation (McCroskery et al. 2003; Garikipati and Rodgers 2012). Myostatin dose-dependently decreases the myotube diameter in C2C12 cells through suppressing PAX3 and PAX7 mRNA levels, which are upstream of MYOD. Also it inhibits Akt, leading upregulation of atrogenes (McCroskery et al. 2003; Rodriguez et al. 2014).

Since myostatin is one of the main sarcopenia-associated factors, myostatin signal inhibitors are under developing. Monoclonal antibodies, directly binding with myostatin such as landogrozumab and binding with the receptor of myostatin such as bimagrumab, neutralize the interaction between myostatin and its receptor (Pouw Kraan et al. 2003; Bechir et al. 2016; Morvan et al. 2017).

HDAC inhibition as potential treatment for sarcopenia

Histone deacetylases (HDACs) play crucial roles in epigenetic regulation in muscles throughout the lifespan (Walsh and Van Remmen 2016). In addition to regulate myogenic gene expressions through histone modification, they can interact with myogenic factors. Class II HDACs (HDAC 4, 5, 7) have been reported to binding with MEF2, a myogenic transcription factor, and inhibit the differentiation of myoblast (Lu et al. 2000; Dressel et al. 2001).

As numerous studies have suggested that HDACs regulate myogenic differentiation, HDACs are regarded as potential targets for treating sarcopenia (Beharry et al. 2014; Walsh and Van Remmen 2016; Luo et al. 2019). In one study, butyrate as an inhibitor of HDACs, regulates the expression of atrogenes and increase mitochondrial biogenesis (Walsh et al. 2015). Another study demonstrates that oral intake of AR-42, a pan-HDAC inhibitor, slows down the progression of atrophy in tumor-bearing mice by inhibiting the expression levels of atrogin-1 and MuRF-1 (Tseng et al. 2015). However, no actual HDAC inhibitors have been used in the clinical trials, and more investigation must be conducted to understand the spatiotemporal mechanisms of HDACs in sarcopenia.

Treatment: non-pharmacotherapy

Since there is no promising pharmacological regimen for sarcopenia in the market yet, patients and clinicians are still counting on non-pharmacological therapy. Numerous methods of exercise and nutritional supports have been suggested. Followings are some of those attempts that gave an impression.

Progressive resistance exercise training

Physical inactivity leads to decreased muscle mass and strength, and the elderly end up in sarcopenic conditions (Peterson et al. 2010). In one study, sarcopenia is reported to be directly associated with the physical activity scale for the elderly (PASE) score, a self-assessment test for the physical activity of older people (Washburn et al. 1999). The PASE score is significantly lower in patients with sarcopenia than in healthy elderly individuals; it is also related to lower muscle mass and strength (Curcio et al. 2019).

Progressive resistance exercise training (PRT) is using muscles against a weight heavier than that used in the previous exercise. This should be performed 2–3 times a week for 8–12 weeks (Ali and Garcia 2014). When appropriately performed, PRT seems to increase muscle strength, muscle size, and functional capacity (Peterson et al. 2010, 2011). It is considered the first choice for the prevention and treatment of sarcopenia, but the lack of experts and equipment makes it difficult to consider it as a common therapy.

Nutritional support

Nutritional support is also considered a possible nonpharmacological treatment, but limited evidence is available. Previous studies have demonstrated that intake of high-quality foods such as protein, vitamin D and antioxidant nutrients had benefits in sarcopenia (Robinson et al. 2018).

One study reports that increased intake of protein helps to overcome anabolic resistance in old mice and elderly patients (Mosoni et al. 2014); however, the details regarding the exact composition of good nutrition or the route of intake remain controversial (Deer and Volpi 2015). Among other amino acids, branched chain amino acids (BCAAs) are known to promote protein synthesis. BCAAs include leucine, valine, and isoleucine, and they are one of essential amino acids.

BCAAs directly promotes protein synthesis via mTOR signaling pathway activation, leading to increase muscle mass (Le Couteur et al. 2020). One study reports that supplementing older people with bigger amount of leucine than in whey protein (26% leucine) lead to increased muscle protein synthesis (Katsanos et al. 2006). Also β-hydroxy-β-methyl butyrate (HMB), a metabolite of leucine, has effect in protein synthesis and mitochondrial dynamics in muscle (Sanz-Paris et al. 2018; Standley et al. 2020; Singh et al. 2021). Oral intake of HMB along with other protein supplements is proven to improve muscle portion in body and maintain muscle mass and function in elderlies (Sanz-Paris et al. 2018).

Several studies have reported that increased intake of proteins and omega-3 improve muscle mass and function as they provide essential nutrition (Smith et al. 2015); however, since the present study is conducted on healthy old people, this cannot infer that nutritional intervention works as a non-pharmacological treatment for sarcopenia patients.

While the effect of nutritional intervention is doubtful, the fact that elderly people tend to have malnutrition is emphasized. Several factors such as changes in eating habits, reduced digestion ability, and physiological anorexia contribute to the prevalence of malnutrition in the elderly (Calvani et al. 2015). This prevalence is approximately 5–20% of malnutrition in community-dwelling elderly and more than 60% in institutionalized elderly people. Sarcopenia can be improved or at least alleviated if adequate energy is provided along with appropriate nutrition such as protein, omega-3, vitamins C and D, creatine monohydrate and antioxidants (Liguori et al. 2018).

Conclusions

Sarcopenia is a skeletal muscle disorder characterized by accelerated loss of muscle mass and function with aging. As society ages rapidly, sarcopenia is associated with a series of socioeconomic burden as well as adverse health outcomes. In this review, we introduce the definition of sarcopenia, the latest integrated diagnosis, underlying mechanisms and developing therapeutic interventions. Although studies on sarcopenia have actively progressed over the last decade, there has been no established therapy for sarcopenia. Based on a clear definition, precise diagnosis criteria and detailed understanding of underlying mechanisms, the strategies for preventing and treating sarcopenia should be developed.

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Declarations

Conflict of interest Sang-Jin Lee is employee of AniMusCure Inc. The remaining authors declares no competing interest.

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