

# Pathophysiology and mechanisms of primary sarcopenia (Review)

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Received April 28, 2021; Accepted June 9, 2021

DOI: 10.3892/ijmm.2021.4989

**Abstract.** Aging causes skeletal muscle atrophy, and myofiber loss can be a critical component of this process. In 1989, Rosenberg emphasized the importance of the loss of skeletal muscle mass that occurs with aging and coined the term 'sarcopenia'. Since then, sarcopenia has attracted considerable attention due to the aging population in developed countries. The presence of sarcopenia is closely related to staggering, falls and even frailty in the elderly, which in turn leads to the need for nursing care. Sarcopenia is often associated with a poor prognosis in the elderly. Therefore, it is crucial to investigate the causes and pathogenesis of sarcopenia, and to develop and introduce interventional strategies in line with these causes and pathogenesis. Sarcopenia can be a primary component of physical frailty. The association between sarcopenia, frailty and locomotive syndrome is complex; however, sarcopenia is a muscle-specific concept that is relatively easy to approach in research. In the elderly, a lack of exercise, malnutrition and hormonal changes lead to neuromuscular junction insufficiency, impaired capillary blood flow, reduced repair and regeneration capacity due to a decrease in the number of muscle satellite cells, the infiltration of inflammatory cells and oxidative stress, resulting in muscle protein degradation exceeding synthesis. In addition, mitochondrial dysfunction causes metabolic abnormalities, such as insulin resistance,

which may lead to quantitative and qualitative abnormalities in skeletal muscle, resulting in sarcopenia. The present review article focuses on age-related primary sarcopenia and outlines its pathogenesis and mechanisms.

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## 1. Introduction

In 1989, Rosenberg (1) emphasized the importance of the loss of skeletal muscle mass that occurs with aging and coined the term 'sarcopenia'. Since then, sarcopenia has attracted considerable attention due to the aging population in developed countries. Lexell *et al* (2) reported that skeletal muscle mass was reduced by ~50% in elderly compared with young individuals, based on analyses using muscles obtained from autopsies. In general, the skeletal muscle area and muscle strength of elderly individuals decreases by 25-30% and 30-40%, respectively, compared with those in their 20s, and muscle mass decreases by 1-2% each year after the age of 50 (3,4). The presence of sarcopenia is closely related to staggering, falls and even frailty in the elderly, which in turn leads to the need for nursing care (3). Therefore, it is crucial to investigate the causes and pathogenesis of sarcopenia, and to develop and introduce interventional strategies in line with these causes and pathogenesis. In addition, nursing care prevention, and medical and nursing care policies also require attention in Japan which has entered a super-aging society (3).

The association between sarcopenia, frailty and locomotive syndrome is complex; however, sarcopenia is a muscle-specific concept that is relatively easy to approach in research. At the organ level, it is known that specific changes in the muscles of the elderly involve a decrease in fast-twitch muscle components and the accumulation of fat in muscles, and at the cellular

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**Abbreviations:** IGF-1, insulin-like growth factor-1; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; GH, growth hormone; PI3K, phosphoinositide 3-kinase; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; ROS, reactive oxygen species; FGF-2, fibroblast growth factor 2; HGF, hepatocyte growth factor; MAPK, mitogen-activated protein kinase; RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme

**Key words:** primary sarcopenia, mechanism, myofiber, satellite cell, myokine

level, a mitochondrial dysfunction occurs (5-7). Age-related sarcopenia is termed primary sarcopenia, and disease-related sarcopenia is termed secondary sarcopenia (8,9). Sarcopenia can be a primary component of physical frailty. Sarcopenia is also a main health concern in the era of the COVID-19 pandemic. Sarcopenia can be an adverse predictor in elderly patients with COVID-19 infection (10,11).

The present review article focuses on age-related primary sarcopenia and outlines its pathogenesis and mechanisms.

## 2. Myofiber and muscle satellite cells

Multiple factors have been proposed to explain the pathogenesis of primary sarcopenia. Myofibers are multinucleated cells formed by the fusion of satellite cells. Skeletal muscle is an organ that is susceptible to damage from overload and trauma; however, it has a notable ability to regenerate. Satellite cells, known as skeletal muscle-specific somatic stem cells, play a central role in the process of muscle regeneration (12-15). Satellite cells are normally dormant; however, when nearby muscle fibers are damaged, they are stimulated by damaged myofibers to become active and form muscle progenitor cells. Cells that proliferate by division fuse with each other or with existing muscle fibers, contributing to the formation, repair and hypertrophy of new myofibers (12-15). Myofibers are classified into two major types (four subtypes) according to the isoform of myosin heavy chain: Type I, IIa, IIx and IIb (16). Myofibers are commanded to contract and relax by neuromuscular junctions, and receive blood flow from surrounding capillaries (5-7). Damaged myofibers are repaired and regenerated by satellite cells, which are bone marrow stem cells (5-7). In addition, mitochondria are abundant in the cells and are involved not only in energy production, mainly through fatty acid beta-oxidation, but also in metabolic regulation, such as insulin sensitivity (15).

The age-related loss of skeletal muscle mass is caused by a decrease in the number of myofibers and the atrophy of individual myofibers, while disuse muscle atrophy due to a long-term bed ridden status and related disuse, which is the cause of secondary sarcopenia, is mainly due to a decrease in the cross-sectional area of myofibers (Table I) (5,14). In disuse atrophy, the time course is acute, the degree is severe, the recovery is often reversible, and the slow-twitch muscles are mainly affected, whereas in primary sarcopenia, the time course is chronic, the degree is mild, the recovery is sometimes irreversible, and the fast-twitch muscles are mainly affected (Table I) (17). As mentioned above, skeletal myofibers are classified into two major types: Type I (slow-twitch fibers) and type II (fast-twitch fibers) fibers, and a decrease in the number of type II fibers is observed from an early stage with aging, eventually resulting in a decrease in the number of both types of myofibers (5,6). The motor neurons that innervate myofibers are located in the spinal cord, and the nerve fibers that emerge from these neurons branch out in multiple directions to reach the muscle fibers (7). The motor neurons and the myofibers they innervate are collectively called motor units, and it is known that these motor units decrease with aging (7). In addition, it has been reported that aging causes morphological changes in neuromuscular synapses, resulting in the functional decline of skeletal muscles and muscle atrophy (18). Muscle satellite cells

exist between the plasma membrane and basement membrane of muscle fibers and are normally dormant; however, they are activated by stimulation, proliferate, differentiate and fuse with existing muscle fibers, playing an important role in muscle regeneration (5-7). Aging causes a loss of function of muscle satellite cells, a decrease in the regenerative capacity of myofibers, and a decrease in the number of myofibers (12,19). Muscle regeneration is maintained by the infiltration of macrophages and the subsequent activation of satellite cells (12). The expression of notch ligand (Delta) is decreased in senescent muscle satellite cells, which may be involved in the decreased proliferative potential of satellite cells (20). In addition, it has been reported that Wnt signaling is also enhanced in senescent satellite cells, which promotes their differentiation into fibrogenic cells (21). The repair process of damaged skeletal muscle from the perspective of muscle satellite cells is illustrated in Fig. 1.

## 3. Protein synthesis and degradation in muscle

The atrophy or hypertrophy of myofibers is dependent on their protein content. Over 80% of the dry weight of muscle is comprised of protein (22). Theoretically, muscle hypertrophy occurs when muscle protein synthesis is increased and degradation is inhibited, while muscle atrophy occurs when degradation is increased and synthesis is inhibited. Muscle protein anabolism in muscle cells is known to be mediated by the following: i) Amino acids (branched chain amino acids, such as leucine); ii) exercise; iii) insulin and insulin-like growth factor-1 (IGF-1); and iv) hormones (23-26). All these factors induce the phosphorylation of mammalian target of rapamycin (mTOR) in myocytes (27). They also exhibit protein anabolism through the activation of 70-kDa ribosomal protein S6 kinase (p70S6K) and eukaryotic initiation factor 4E binding protein-1 (4E-BP1) (27).

The mTOR complex 1 (mTORC1) signaling pathway is a major regulator of protein metabolism (28). mTORC1 regulates protein synthesis and degradation by integrating a number of intracellular signals (28). For example, leucine intake and exercise activate mTORC1, leading to increased protein synthesis. On the other hand, during fasting, mTORC1 is inactivated and protein degradation is enhanced (28). The age-related loss of skeletal muscle mass is less likely to lead to the diet-induced enhancement of protein synthesis in the elderly due to the decreased sensitivity of mTORC1 to leucine (29). It has been shown that leucine is not only an organelle of muscle proteins, but also acts directly on muscle cells to induce protein synthesis (13). In addition, IGF-1, a potent anabolic factor, is regulated by growth hormone (GH) and is produced mainly in the liver (30). Ghrelin, a GH-promoting peptide, not only promotes GH secretion, but also has the function of promoting central or peripheral feeding (31). IGF-1 is involved in a number of anabolic pathways in skeletal muscle, including cell proliferation, differentiation and metabolism and muscle regeneration (32,33). As mentioned above, one of the causes of sarcopenia is decreased muscle synthesis; IGF-1 activates the intracellular signaling pathways of phosphoinositide3-kinase (PI3K) and Akt, and further activates downstream mTOR, which enhances protein synthesis (34,35). The IGF-1/PI3K/mTOR system is important in muscle

Table I. Clinical and pathophysiological features of primary sarcopenia and disuse muscle atrophy.

Feature	Primary sarcopenia	Disuse muscle atrophy
Clinical course	Chronic	Acute
Degree of muscle damage	Mild	Severe
Recovery	Sometimes irreversible	Often reversible
Mainly affected muscle	Fast-twitch muscles	Slow-twitch muscles
Myofiber	Decrease in the number of myofiber. A decrease in the number of type II fibers is observed from an early stage with aging	Decrease in the cross-sectional area of myofibers
Motor neuron function	Often damaged	Often maintained

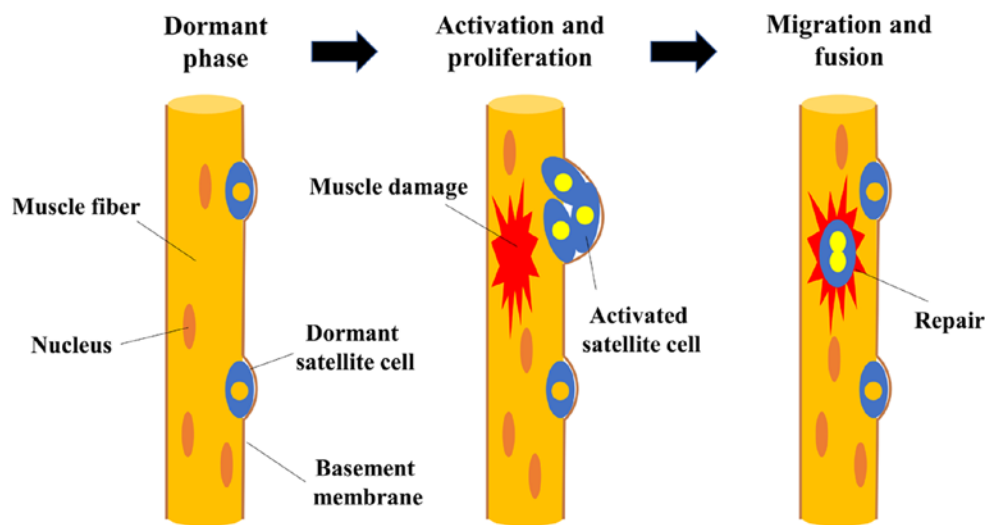


Figure 1. Muscle satellite cells during muscle regeneration. Muscle satellite cells reside between the muscle cell membrane and the basement membrane, and they are dormant. When a muscle fiber is damaged, satellite cells are activated, proliferate, and fuse to the muscle fiber to repair the damaged area. Some of the activated satellite cells return to their dormant state.

hypertrophy; however, its activity decreases with aging (36). The second is the enhancement of muscle breakdown. Ubiquitin is an approximately 8.5-kDa protein with a high degree of sequence conservation among different species and exists in a ubiquitinated (ubiquitylation, a type of protein modification) state (37,38). When a protein is ubiquitinated in the cell, the proteasome is able to degrade it. In 2001, the muscle-specific ubiquitin ligase genes, muscle-specific RING finger protein 1 (MuRF1) and Atrogin-1 (muscle atrophy-related factors), were identified (37,38). Atrogin-1 is encoded by the Fbxo32 gene, which is also referred to as a muscle atrophy-related factor, and is upregulated in a wide range of pathological conditions, such as neurectomy and disuse; however, mice in which Atrogin-1 is knocked out are less susceptible to neurectomy-induced muscle atrophy (37).

It has also been reported that muscle atrophy-related factor is increased in skeletal muscle of elderly individuals and aging rats (39,40). Protein synthesis in muscle decreases with aging, and protein anabolism is suppressed in the muscles of the elderly even when the same amounts of amino acids are present in the blood (i.e., anabolic resistance) (41). The

mTOR activation response to amino acids, such as leucine that can stimulate mTOR phosphorylation is reduced in the elderly (41,42).

#### 4. Immunological dysfunction and inflammation with aging

Elderly individuals are more likely to develop chronic inflammation, which is a persistent mild inflammation, due to the decline in immune function caused by aging. The risk of developing inflammatory diseases, such as infections and collagen diseases is increased in the elderly with an impaired immune function (43). These chronic inflammations are characterized by mildly elevated blood levels of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-6 and IL-18. C-reactive protein (CRP), an acute-phase protein produced by the liver in response to IL-6, is also upregulated during chronic inflammation (44). Blood levels of TNF- $\alpha$ , IL-1  $\beta$ , and IL-6 have been reported to increase 2- to 4-fold in the elderly compared with healthy young adults (45). It has been also shown that the administration

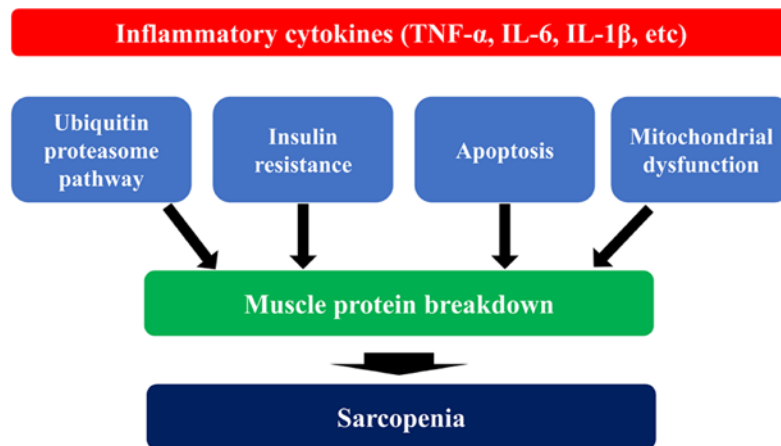


Figure 2. Inflammatory cytokines and sarcopenia. TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL, interleukin.

of IL-6 and TNF- $\alpha$  to rats causes the degradation of skeletal muscle (46,47). Inflammatory cytokines cause the dysfunction of mitochondria, which are involved in energy production, resulting in a decreased ATP production, as well as in the excessive production of reactive oxygen species (ROS) (48,49). Excessive ROS production further exacerbates mitochondrial damage and subsequent metabolic abnormalities, and induces proteolysis by enhancing the ubiquitin-proteasome system, one of the major pathways for protein degradation as described above, resulting in skeletal muscle atrophy (50,51). Proteins labeled with ubiquitin are degraded by the proteasome, a large enzyme complex (52). Apoptosis, on the other hand, is a cell death mechanism that removes unnecessary cells. The activation of caspases, proteolytic enzymes, rapidly degrades intracellular proteins, which are ultimately phagocytosed by macrophages and other phagocytic cells (53). TNF- $\alpha$  is a major regulator of the apoptotic signaling pathway. TNF- $\alpha$  binds to TNF- $\alpha$  receptors in skeletal muscle and activates caspases through the Fas-associated death domain (FADD), thereby inducing apoptosis (54). Excessive apoptosis in skeletal muscle leads to increased degradation of muscle proteins, resulting in muscle atrophy (55).

Obesity is another important factor in the development of chronic inflammation. In recent years, it has been shown that adipose tissue interacts with immune cells, such as macrophages and neutrophils to induce chronic inflammation in obese individuals (56). TNF- $\alpha$  secreted by macrophages increases free fatty acids by promoting lipolysis through the Toll-like receptor 4 (TLR4) signaling pathway in adipose tissue (56). In addition, the macrophage response to free fatty acids increases the secretion of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6, further exacerbating chronic inflammation (57). Inflammation-associated immune cell infiltration is found not only in adipose tissue, but also in skeletal muscle; in a study on critically ill hospitalized patients aged 50-59 years, the increased infiltration of CD68-positive macrophages into skeletal muscle was observed with atrophy of the rectus femoris muscle after 7 days of hospitalization (58). Thus, chronic inflammation induced by various factors in aging is considered to reduce muscle strength and function by increasing macrophage infiltration into skeletal muscle, decreasing muscle mass and increasing the accumulation of

ectopic fat (59). Recently, sarcopenic obesity, a condition that involves both sarcopenia and obesity, has been attracting attention. Patients with sarcopenic obesity have a poorer prognosis than those with sarcopenia alone or obesity alone (60). The association between inflammatory cytokines and sarcopenia is illustrated in Fig. 2.

## 5. Myokines and sarcopenia

Biologically active substances produced by muscle cells are termed myokines, and IGF-1, IL-6, fibroblast growth factor 2 (FGF-2), hepatocyte growth factor (HGF) and IL-15 are representative myokines (61,62). Some myokines act endocrinologically on organs throughout the body (e.g., pancreas, brain, adipose tissue), while others act paracrine or autocrine on skeletal muscle itself (61,62). Pedersen *et al* (63) defined myokines as 'cytokines and peptides expressed in and secreted from skeletal myofibers that act in a paracrine and endocrine manner'. Myokines released from damaged myofibers act as messengers in the process of muscle regeneration by satellite cells upon muscle injury. When myofibers are damaged, cytokines and chemokines are first secreted by macrophages that migrate to the damaged area, and growth factors are also released from the damaged myofibers, which act on satellite cells to initiate muscle regeneration (64). Growth factors play a role in regulating the proliferation and differentiation of satellite cells (64). The expression of IGF-1 has also been found in skeletal muscle, where it is released from myofibers upon stimuli that damage the cell membrane, such as muscle overload (65). IL-6 is the oldest known myokine molecule, and its physiological effects include systemic metabolic regulation (66). HGF is also released extracellularly upon muscle injury and activates satellite cells (67). HGF activates mTOR signaling (68). FGF-2 is another growth factor that is secreted upon cell membrane damage (69,70). FGF-2 plays a role in regulating cell proliferation and differentiation by activating the mitogen-activated protein kinase (MAPK) signaling pathway in many cells (71). In satellite cells, p38 $\alpha$ / $\beta$ MAPK is activated upon entry from quiescence into the cell cycle, which is triggered by FGF-2 (62). It has also been shown that the activation of the Erk1/2 pathway by FGF-2 is essential in proliferating myocytes between G1 and S phases of the cell

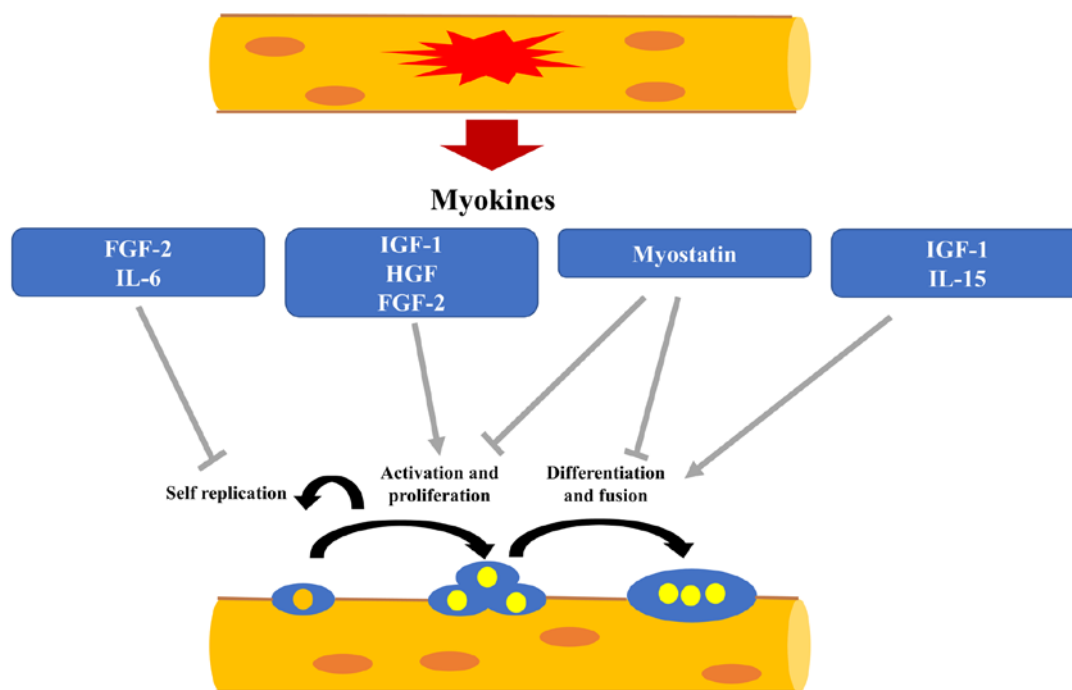


Figure 3. Role of myokines associated with the regulation for the functions of muscle satellite cells. FGF-2, fibroblast growth factor 2; IL, interleukin; IGF-1, insulin-like growth factor-1; HGF, hepatocyte growth factor.

cycle (72). IL-15 is a cytokine that is abundantly expressed in skeletal muscle and is recognized as a myokine that acts endocrinologically on adipose tissue and regulates whole body energy metabolism (73). On the other hand, IL-15 has anabolic effects and is considered to be involved in skeletal muscle hypertrophy (74). It has been shown that the muscle hypertrophic effect of IL-15 occurs in a pathway independent of IGF-1 (75). When cultured skeletal muscle cells are treated with IL-15, protein synthesis is increased and protein degradation is inhibited, resulting in hypertrophy of muscle fibers (75,76). While, it has been reported that the number of satellite cells decreases with aging, suggesting a link to reduced muscle regeneration capacity (77). This is attributed to the reduced self-replication capacity of satellite cells due to aging and the inability to secure the number of stem cells. On the other hand, myokines are also considered to play a part in the mechanism of inhibiting cancer growth by exercise, and one myokine that has actually been shown to inhibit cancer growth is secreted protein acidic and rich in cysteine (SPARC) (78).

Myostatin is a myokine that belongs to the TGF-family. In 1997, it was reported that skeletal muscle mass markedly increased in myostatin gene-knockout mice, which attracted attention as a factor regulating muscle mass (79). Myostatin binds to activin type IIB receptor and ALK4/ALK5 coreceptor, promotes phosphorylation of Smad2 and Smad3 proteins, and suppresses the expression of genes involved in skeletal muscle differentiation (80,81). Myostatin has also been reported to inhibit the PI3K/Akt signaling pathway (82). It has also been reported that myostatin secretion from muscle and adipocytes is increased in patients with severe obesity (83), and that weight loss decreases the expression of myostatin in muscle (84). Sarcopenic obesity can be associated with these observations. Follistatin and follistatin-related genes are known to be molecules that bind to and inhibit the function

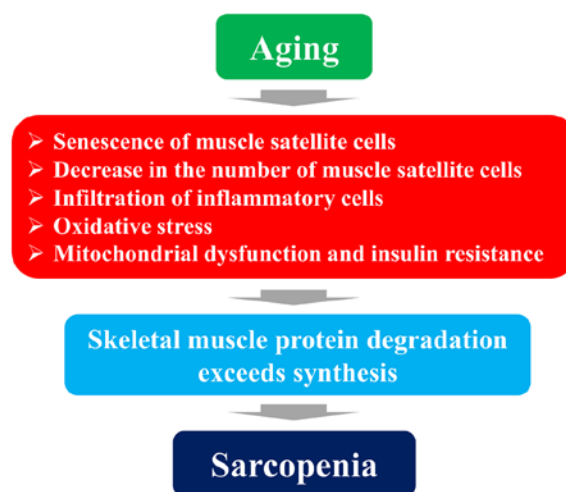


Figure 4. Schematic diagram of the pathogenesis of sarcopenia during the aging process.

of myostatin, and it is expected that these molecules can be used to increase muscle mass (85). During high-intensity exercise, myostatin is suppressed and muscle hypertrophy can occur through activation of the mTOR/IGF-1 system (86). The schematic explanation between myokines associated with the regulation for the functions of muscle satellite cells and the repair of damaged myofiber is illustrated in Fig. 3.

In recent years, it has also become clear that the myostatin gene is involved in the 'appropriateness for the running distance' of racing horses (87). There are three genetically distinct types of myostatin (C/C, C/T and T/T) in Thoroughbreds (88). It has been found that the difference of genetic types is associated with muscle mass and appropriateness for the running distance. In the C/C type muscle mass

tends to increase slightly, in the T/T type it tends to decrease slightly, and in the C/T type it tends to be in the middle (88). Therefore, racing horses with the C/C type tends to be suitable for a short distance, while those with the T/T type tends to be suitable for medium and long distances. Those with the C/T type tends to be suitable for a medium distance (88).

## 6. Renin-angiotensin system, sex hormones and sarcopenia

The renin-angiotensin system (RAS) is known from a report published in the *Lancet* in 2002, which demonstrated that continuous angiotensin-converting enzyme (ACE) inhibitor treatment suppressed knee extensor strength decline and walking speed decline (89). This report attracted attention to the suppression of the RAS. RAS activation is thought to cause sarcopenia through the following: i) Indirect effects, such as angiotensin II-induced decrease in anabolic hormones, induction of proinflammatory cytokines and increased muscle protein degradation via increased myostatin; and ii) direct oxidative stress via angiotensin II type I receptors (90,91). RAS suppression may contribute to the prevention of sarcopenia.

Age-related changes in reproductive endocrine organs are considered to be one of the most important functional changes associated with aging. In general, thyroid hormones and glucocorticoids maintain relatively constant levels in response to aging, whereas blood levels of sex steroid hormones, such as testosterone, are known to decrease with age in adults (92,93). The decline in blood testosterone levels with aging is considered to be associated with geriatric diseases and functional disabilities. In a cross-sectional study on men aged 24-90 years, serum testosterone levels were reported to be positively associated with skeletal muscle mass and muscle strength (94). In post-menopausal women, estrogen decline can cause endocrine and metabolic dysfunction, resulting in a predisposition to osteoporosis, metabolic syndrome and sarcopenia (95). Osteosarcopenia, a combined condition of osteoporosis and sarcopenia, increases the risk of developing frailty (96).

## 7. Conclusions

The present review outlined the pathogenesis of primary sarcopenia from the following viewpoints: i) Myofibers and muscle satellite cells; ii) protein synthesis and degradation; iii) immunocompetence and inflammation; iv) myokines; v) RAS; and vi) sex hormones. In the elderly, a lack of exercise, malnutrition and hormonal changes lead to neuromuscular junction insufficiency, an impaired capillary blood flow, a reduced repair and regeneration capacity due to the senescence of muscle satellite cells, a decrease in the number of muscle satellite cells, the infiltration of inflammatory cells and oxidative stress, resulting in muscle protein degradation exceeding synthesis. In addition, mitochondrial dysfunction causes metabolic abnormalities, such as insulin resistance, which may lead to quantitative and qualitative abnormalities in skeletal muscle, resulting in sarcopenia. A schematic diagram of the pathogenesis of sarcopenia during aging process is illustrated in Fig. 4. Skeletal muscle has been the subject of a great amount of research in recent years, and it is hoped that further drug discovery for sarcopenia based on pathological conditions will be developed in the future. The authors consider

that the novelty of the present review article is that it outlines the pathogenesis of sarcopenia based on the latest evidence, with the aim of assisting in the development of novel drugs for sarcopenia.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

Not applicable.

## Authors' contributions

HN wrote the review article. SF, AA, KY, SN and KH were involved in the editing and reviewing of the article. HN and KH confirm the authenticity of all the raw data. All authors have read and approved the final article.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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