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Current Status of Sarcopenia in Korea: A Focus on Korean Geripausal Women

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Sarcopenia is defined as an age-associated decline in muscle mass and function caused by several etiologies and mechanisms. Muscle mass and function do not decrease concurrently, and a loss of muscle function may be more highly associated with adverse health outcomes. Despite the clinical significance of sarcopenia, no universally operational definition of sarcopenia or standardized intervention programs are currently available. Sarcopenia, osteoporosis, and obesity share several pathophysiological mechanisms, and a combination of these entities may lead to an increased risk of musculoskeletal, cardiometabolic, and psychological morbidities especially in geripause populations. Treatment for sarcopenia is mainly nonpharmacological, however, various drugs are currently being developed. It is conceivable that sarcopenia is the next immediate clinical target in musculoskeletal science. **(Ann Geriatr Med Res 2018;22:52-61)**

Key Words: Sarcopenia, Geripause, Muscle wasting, Korea

INTRODUCTION

The human body is composed of 3 compartments; namely fat, lean tissue (fat-free), and bone. Among these, lean body mass declines most dramatically and is functionally significant. Skeletal muscle makes up 45%–50% of the body mass. It is a dynamic tissue in which the mass and function decline linearly with age.[1]

The term "sarcopenia or sarcomalacia," derived from the Greek, was first proposed by Rosenberg in 1989 to describe age-related loss of muscle mass.[1] However, in addition to aging, muscle loss is also caused by a number of etiologies such as disease, decreased activity level, and nutritional disturbance. Therefore, "myopenia" was proposed to describe this condition.[2]

Since muscle mass and function do not decrease concurrently and a loss of muscle function may be more highly associated with adverse health outcomes such as physical disability, fall, fracture and mortality than that of muscle mass, muscle strength may be a superior indicator of general muscular dysfunction. The term dynapenia or kratopenia was also proposed to specifically describe the loss of muscle function.[3-5]

Lastly, the term "muscle wasting disease" was recently suggested as a new disease classification to describe the disease etiology and progression.[6] However, sarcopenia is a widely accepted term and is currently used more broadly to describe the age-associated loss in muscle mass and function (Table 1).

Sarcopenia was recently recognized as an independent condition in the International Classification of Disease, 10th revision, Clinical Modification (ICD-10-CM). The assigned code, M62.84, has been available for use in the US alone since October 1, 2016.[7]

MUSCLE CHANGES WITH AGING

1. Satellite Cells

Satellite cells maintain skeletal muscle homeostasis and enable skeletal muscle regeneration.[8] The number of satellite cells declines with age, especially in muscle fibers expressing type II myosin heavy chain.[9] Moreover, the activation of satellite cells in response to muscle damage

Table 1. Terms related to sarcopenia

Loss of muscle	Reference
Age-related	
Mass	
Sarcopenia	Rosenberg (1989)[1]
Strength	
Dynapenia	Clark and Manini (2008)[3]
Kratopenia	Morley et al. (2011)[4]
Age- /non–age-related	
Myopenia	Fearon et al. (2011)[2]
Skeletal muscle function deficit	Correa-de-Araujo and Hardley (2014)[5]
Muscle wasting disease	Anker et al. (2014)[6]

may be blunted in older adult men. A positive regulator of satellite cell proliferation, interleukin-6 (IL-6), mediates this phenomenon. With age, however, levels of IL-6 are chronically elevated, which promotes muscle catabolism by suppressing cytokine signaling proteins. These events weaken the efficacy of anabolic signaling pathways including insulin-like growth factor 1 (IGF-1).[10]

2. Muscle Fibers

1) Quantitative changes in muscle fiber: decline in muscle mass

The decline in muscle mass is accompanied by a 30%–40% decrease in the number and size of muscle fibers between the second and the eighth decades.[11] By 12 to 15 years of age, the muscle fibers reach the normal adult size. The aging-related decline in muscle fiber size is fiber-type specific. Compared to young controls, type II fibers are 10%–40% smaller in the elderly.[12] In contrast, the size of type I muscle fibers is principally unaffected.[9]

2) Qualitative changes in muscle fiber: decline in muscle strength

The aging-related decline in muscle strength can be explained by reductions in the intrinsic force-generating capacity of skeletal muscle fibers. Aging-related alterations in cellular and molecular processes are associated with the mechanism of reduced muscle strength.[10]

3) Fiber type transformation

Aging results in the transformation from fast to slow-twitch muscle fibers.[13]

4) Excitation-contraction coupling

Aging causes a reduction in the number of dihydropyridine receptors, uncoupling between these receptors and ryanodine receptors, and deficits in calcium release. Consequently, this phenomenon causes uncoupling of the excitation-contraction process, which results in reduced muscle fiber activation, force generation, and lower whole muscle strength.[14,15]

5) Myofilament aging

Single-fiber maximal force is reduced in both type I and II fibers in old age. A decrease in myosin protein content partly explains this dysfunction.[16] Moreover, increased instantaneous stiffness has been reported not only in single fibers but also in whole muscle.[17]

6) Adipocyte infiltration

With aging, both intramuscular and intermuscular adipose tissues are increased. Consequently, increased muscle fat infiltration is associated with a decline in muscle strength.[18]

7) Mitochondrial function

Age-related alterations in muscle cell organelles such as the loss of mitochondrial content and function result in muscle dysfunction.[19]

Therefore, a decline in muscle quality is more important than a decline in muscle mass in elderly populations.

3. Changes in Muscle Mass and Strength With Aging

A progressive loss of muscle mass and strength occurs from approximately 40 years of age. This loss has been estimated at about 8% per decade until the age of 70 years, after which the loss increases to 15% per decade. This loss causes a 40% decrease in muscle circumference from 30 to 60 years of age. A 10%–15% loss of leg strength per decade is seen until 70 years of age, after which a faster loss, ranging from 25% to 40% by decade, occurs (Table 2).[20] As a result, muscle mass decreases by nearly 50% from 20 to 90 years of age. Although muscle mass loss is greater in men than that in women, the public health concern is greater in women because the average lifespan of women is longer than that of men.

CLINICAL CONSEQUENCES

Sarcopenia in older populations is related to falls, functional impairment, loss of independence, increased mortality, and poor quality of life.[21]

Age-related decrease in muscle mass and strength may lead to reduced physical activity. A reduction in muscle mass and physical activity reduces the total energy expenditure and may lead to weight gain and obesity. As a result, sarcopenia and obesity are associated with a worsened pulmonary function. Furthermore, the association between obesity, metabolic alterations, and cardiovascular disease has been observed even at older ages.[22] Sarcopenia has also been associated with depressive mood.[23] Together, these observations suggest that sarcopenia increases the risk of musculoskeletal, cardio-metabolic, and psychological morbidities.

The negative health outcomes, including mobility limitation, fall, fracture, hospitalization, poor quality of life, and mortality, had a more significant relationship to the decline in muscle strength than that of muscle mass. Therefore, a loss of muscle strength has more clinical implications than a loss of muscle mass and these 2 conditions should be considered independently.[15]

The nervous system also contributes to increased or decreased muscle strength. Both neurological and muscular factors may lead to sarcopenia.[3]

Table 2. Changes in muscle mass and strength with age based on 40s

Age (yr)	Loss of muscle mass	Loss of muscle strength
Until 70	8%/decade	10%–15%/decade
After 70	15%/decade	25%–40%/decade

CLINICAL DIAGNOSIS

1. European Working Group on Sarcopenia in Older People

The European Working Group on Sarcopenia in Older People (EWGSOP) suggests a practical clinical definition and consensus diagnostic criteria for sarcopenia and recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia.

The EWGSOP suggests a conceptual staging in three grades. The 'presarcopenia' stage is characterized by low muscle mass without impact on muscle strength or physical performance. The 'sarcopenia' stage is characterized by low muscle mass plus low muscle strength or low physical performance. Finally, the 'severe sarcopenia' stage is defined as the condition in which all three criteria are met.

Appendicular skeletal muscle mass (ASM) is calculated by summing the muscle mass of the four limbs from dual-energy x-ray absorptiometry (DXA) scan. The skeletal muscle index (SMI) is calculated as ASM/height (m)^2. The suggested cutoff values are 7.26 kg/m^2 in men and 5.5 kg/m^2 in women by DXA. Low handgrip strength is defined as <30 kg for men and <20 kg for women. Low physical performance is defined as a gait speed ≤0.8 m/sec (Table 3).[24]

2. Asian Working Group for Sarcopenia

In principle, the Asian Working Group for Sarcopenia (AWGS) follows the diagnostic approach of EWGSOP, with the addition of Asian perspectives in sarcopenia diagnosis and research. For Asian populations, the AWGS recommends using height-adjusted skeletal muscle mass instead of weight-adjusted skeletal muscle mass, with suggested cutoff values of 7.0 kg/m^2 in men and 5.4 kg/m^2 in women by DXA. By bioimpedance analysis (BIA), the suggested cutoffs are 7.0 kg/m^2 in men and 5.7 kg/m^2 in women, as defined by SMI. To evaluate muscle strength, the AWGS defines low handgrip strength as <26 kg and <18 kg for men and women, respectively. Gait speeds <0.8 m/sec was defined as low physical performance (Table 3).[25]

Table 3. Cutoffs for the diagnosis of sarcopenia

Variable	EWGSOP	AWGS
Skeletal muscle index (kg/m^2)		
DXA		
Male	7.2	7.0
Female	5.5	5.4
BIA		
Male	-	7.0
Female	-	5.7
Handgrip strength (kg)		
Male	30.0	26.0
Female	20.0	18.0
Gait speed (m/sec)	0.8	0.8

EWGSOP, European Working Group on Sarcopenia in Older People; AWGS, Asian Working Group for Sarcopenia; DXA, dual-energy x-ray absorptiometry; BIA, bioimpedance analysis.

3. Foundation for the National Institutes of Health

The Foundation for the National Institutes of Health (FNIH) defines mobility impairment as gait speed <0.8 m/sec. The FNIH uses an approach based on the paradigm of clinicians making differential diagnosis among older adults with physical limitations. They recommend a set of sex-specific, derived cutoffs for low absolute grip strength and low appendicular lean mass (DXA) standardized to body mass index (BMI) as potential criteria for clinically relevant weakness and low lean mass, respectively, in older men and women (Table 4).[26]

4. Diagnostic Criteria in Korea

1) SMI in Korean women

According to a previous study including 11,633 women aged 10 to 97 years based on data obtained from the 2008 to 2011 Korean National Health and Nutrition Examination Survey (KNHANES), the SMI of women in their 30s and 40s showed a peak ASM (Fig. 1). This finding was quite different from those of the EWGSOP or AWGS study which showed a peak ASM in the 20s and 30s. The mean and standard deviation of SMI in the 30s and 40s was 5.9±0.7 kg/m^2 and the cutoff of 4.4 kg/m^2 was defined according to two standard deviations below the mean SMI. Because the cutoff in this study was markedly lower than that of previous reports, further study is needed.[27]

2) Prevalence of sarcopenia in Korean women

The prevalence of sarcopenia can vary depending on the definitions used. The prevalence of sarcopenia was 0.1% when using the height-adjusted definition and 9.7% when using the weight-adjusted definition in a study on the prevalence of sarcopenia using KNHANES data.[28] Another study, which was part of the Korean Sarcopenic Obesity Study, reported a sarcopenia prevalence of 4.1% and 14.2% using the height-adjusted and weight-adjusted indexes, respectively.[29]

According to a previous study including 11,633 women

Table 4. FNIH Sarcopenia Project: recommended criteria for clinically relevant weakness and low muscle mass

Criterion	Measure	Cutoff	
		Men	Women
Physical limitation	Gait speed (m/sec)	0.8	0.8
Primary			
Weakness	HGS (kg)	26	16
Low muscle mass	ALM (DXA)/BMI	<0.789	<0.512
Alternate			
Weakness	HGS/BMI	<1.0	<0.56
Low muscle mass	ALM (DXA) (kg)	<19.75	<15.02

FNIH, Foundation for the National Institutes of Health; HGS, hand grip strength; ALM, appendicular lean mass; DXA, dual-energy x-ray absorptiometry; BMI, body mass index.

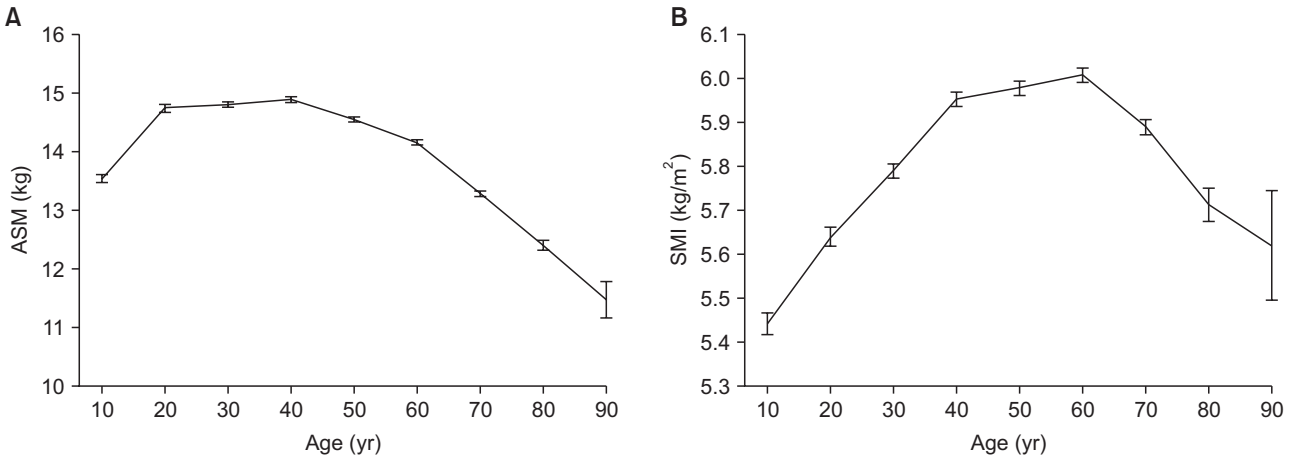

Fig. 1. (A) Distributions of appendicular skeletal muscle mass (ASM), showing a peak in the 40s. (B) Distributions of skeletal mass index (SMI), showing a peak in the 60s.[27]

using data obtained from the 2008 to 2011 KNHANES and using 5.4 kg/m^2 as the SMI cutoff, the prevalence rate of low muscle mass was 22.1% in healthy elderly women ≥65 years of age. Furthermore, the prevalence rates are markedly increasing according to the age.[30]

Another study of 196 ambulatory women over 65 years of age who visited the University Hospital Menopause Clinic showed that 20.9% of participants had low muscle mass and a sarcopenia prevalence rate of 7.6% based on the cutoff values proposed by the AWGS. The sarcopenia stage also intensified with aging.[31]

EMERGING ISSUES IN SARCOPENIA

1. Sarcopenia Biomarkers

Maintenance of normal muscle mass and function depend on a balance between the positive and negative regulators of muscle growth. The shift in this balance to muscle growth inhibitors is one of the main mechanisms underlying sarcopenia pathogenesis. In other words, the prevalence of negative regulators of muscle growth, such as transforming growth factor-beta (TGF-β), myostatin, activins A and B, and growth and differentiation factor-15 (GDF-15) over positive regulators including bone morphogenetic proteins, brain-derived neurotrophic factor, follistatin, and irisin result in sarcopenia and may, thus, be biomarkers of sarcopenia. In addition, processes such as chronic low-grade inflammation (inflamm-aging), accompanied by elevated circulating levels of some pro-inflammatory cytokines, mainly IL-6; neuromuscular junction (NMJ) dysfunction characterized by the appearance of the C-terminal agrin fragment in the NMJ; as well as contractile insufficiency followed by the appearance of tropomyosin-binding subunit troponin – skeletal muscle-specific troponin T are also most likely the key elements of sarcopenia.[32]

2. Muscle-Bone Crosstalk

Muscle secreted myokines such as IGF-1 and fibroblast growth factor-2 enhance bone synthesis, while growth differentiation factor-8 (myostatin) inhibits it. On the other hand, osteocyte-derived molecules such as sclerostin and osteoblast-derived molecules such as osteocalcin may have an effect on muscles because of osteocyte dendrite, which is directly connected to muscles.[33,34]

Recently, cartilage, adipose tissue, and tendons have been proposed to affect bone and muscle and, in turn, can be affected by these tissues.[33]

3. Sarco-osteoporosis

In old age, sarcopenia and osteoporosis show a high prevalence and lead to a high risk for falls, fractures, and further functional decline. These are associated with similar risk factors including genetics, endocrine function, and mechanical factors.[35] Individuals with a combination of both disorders, called 'sarco-osteoporosis,' are at the greatest risk of falls and fractures.[36,37]

4. Sarcopenic Obesity

The concurrence of both obesity and sarcopenia, sarcopenic obesity (SO), purportedly increases the risk of metabolic syndrome, physical disability, morbidity, and mortality more than either sarcopenia or obesity alone.[38] Age-related decrease in muscle mass and strength may lead to reduced physical activity. Decreased muscle mass and physical activity reduces the total energy expenditure and may result in weight gain and obesity.

Obese conditions induce inflammatory signaling pathways in metabolic cells through several pathways, leading to subacute low-grade inflammation. Adipocytes play a role as immune cells and are able to synthesize and release large amounts of proinflammatory adipokines and cytokines such as leptin, resistin, plasminogen activator inhibitor-1, IL-6, tumor necrosis factor-α, retinol-binding protein 4, IL-1β, and more recently described cytokines including IL-18 and IL-33.[39] Inflammation induced by these adipokines can influence muscle metabolism and contrib-

utes to the development of sarcopenia. Furthermore, adipokines associated with insulin resistance, energy metabolism, and growth hormone secretion result in progressive muscle atrophy and fat accumulation.[40]

Central obesity can influence the decline in both muscle quality and muscle quantity that leads to sarcopenia. The degree of myofibrosis and myosteatosis that are the main predictors of quality of muscles is associated with aging and a pattern of increased adiposity.[41] Aging of skeletal muscle is associated not only with muscle atrophy and replacement of muscle by adipose tissue but also with an increase in fibrous connective tissue; similar results have been observed in obese condition.[41]

In general, patients with sarcopenia have low weight and low BMI. In contrast, patients with SO have high weight, low lean body mass, and high BMI. The combination of low lean body mass and obesity may result in physical immobility and more severe disorders. Thus, future investigation is necessary to establish the consensus definition of SO and to promote the standardized diagnosis for the management of SO.

5. Dysmobility Syndrome

With aging, changes in muscle, fat, and bony tissues lead to 'osteosarcopenic obesity,' a term coined to describe the co-occurrence of the 3 phenotypes, osteopenia/osteoporosis, sarcopenia, and obesity. Osteosarcopenic obesity results in impaired physical ability and increased risk of falls and fractures. This condition is associated with poorer functional and metabolic outcomes than each of these conditions alone, ultimately affecting the quality of life, morbidity risk, and survival (Fig. 2).[42,43]

Binkley et al.[44] proposed a new condition, dysmobility syndrome, which comprehensively considers bone, muscle, and fat for the early identification of older people at risk. Dysmobility syndrome is defined using a score-based approach. People with three or more of the following conditions were considered to have dysmobility syndrome; i.e., osteoporosis, low lean mass, history of falls within the past year, slow gait speed, low grip strength, and high fat mass. Several cross-sectional studies have demonstrated associations between previous fractures and dysmobility syndrome and have supported that dysmobility syndrome significantly predicts mortality.[45]

TREATMENT OF SARCOPENIA

At present, the gold standards for increasing muscle function remain exercise and nutrition, despite a number of interventions.

1. Exercise

Exercise interventions including resistance and aerobic exercise have a role in increasing muscle strength and improving physical performance via various mechanisms. Moreover, exercise has been shown to safely improve other common conditions in adults and older patients.[46,47] The American College of Sports Medicine and the American Heart Association recommend weight training 2 or 3 times a week to for increased muscle size and strength, even in frail older persons.[48] However, many forms of physical activity are too intense for older adults to maintain over an extended period of time. Therefore, new exercise technique such as low-intensity vibration has been suggested and may also be attractive to subjects otherwise unable or unwilling to exercise conventionally; however, the effectiveness of this exercise remains controversial.[49]

2. Nutrition

1) Protein intake

With aging, a number of factors may lead to an imbalance between anabolic and catabolic processes, which results in muscle protein breakdown and sarcopenia. Optimal muscle protein metabolism is highly dependent upon an adequate intake of dietary-derived proteins and amino acids.[50] Although aged muscles have a reduced ability to up-regulate protein synthesis, muscles from older individuals retain the capacity to mount a robust anabolic response following the ingestion of protein-rich meals.[51]

Adequate protein and energy intake together with physical exercise is the most effective strategy currently available for the management of sarcopenia.[52] Recent guidelines from the PROT-AGE Study Group and the European Society for Clinical Nutrition and Metabolism recommend a higher average daily intake, in the range of 1.0–1.2 g/kg body weight/day in healthy older persons aged >65

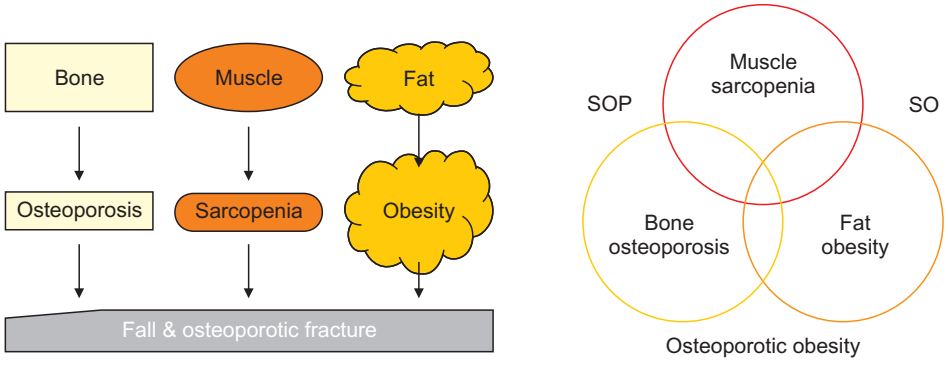

Fig. 2. Dysmobility syndrome. SOP, sarco-osteoporosis; SO, sarcopenic obesity.

years.[53,54] Thus, a dietary plan that includes 25–30 g of high-quality protein, especially leucine-enriched and balanced essential amino acids, per meal may be optimal to maximize muscle protein synthesis in persons with sarcopenia.[55]

2) Vitamin D and calcium intake

Vitamin D has multiple effects on skeletal muscle and also regulates a number of other cell functions that may affect skeletal muscle mass and strength. Vitamin D increases calcium uptake in muscle cells and has a regulatory effect on the calcium channel, which is important for muscle contractile activity. Vitamin D promotes muscle protein synthesis and calcium and phosphate transport in muscle, thus influencing muscle strength. It also appears to optimize the effect of dietary proteins on skeletal muscle anabolism. The identification of vitamin D receptors in skeletal muscle cells provides evidence for a direct mechanism by which vitamin D acts on skeletal muscle.[56]

Guidelines from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) propose optimized recommended nutrient intakes for calcium (1,000 mg/day) and vitamin D (800 IU/day).[57] In addition, the ESCEO recommends vitamin D supplementation at 800–1,000 IU/day to maintain serum 25-(OH) D concentrations >50 nmol/L (>20 ng/mL) in elderly or postmenopausal women at risk of vitamin D deficiency.[58]

3. Hormone Replacement Therapy

Experimental studies indicate that skeletal muscle is an estrogen-responsive tissue. A decline in estrogen results in decreasing muscle mass and function. Muscle strength and power are correlated with estrogen levels and a significant decrease in muscle power occurs in postmenopausal women. Estradiol acts through estrogen receptors in skeletal muscle to improve the function of myosin and ultimately improve muscle strength.[59] Thus, hormone replacement therapy appears to be associated with greater muscle power, regulation of muscle contraction, and favorable muscle composition among younger postmenopausal women.[56]

MEDICATIONS

1. Hormonal Therapy

1) Testosterone

From 30 years of age, testosterone levels decline at the rate of 1% per year in men. This decline is associated with a decline in muscle mass and strength.[60,61] Testosterone not only increases muscle mass and power but also decreases fat mass in elderly men.[62,63] Thus, testosterone therapy is recommended for those with low muscle mass and function as symptoms or signs of testosterone deficiency.

2) Selective androgen receptor modulators

There is concern that testosterone may produce excessive side effects, which has driven the exploration for selective androgen receptor modulators (SARMs), which are theoretically safer. SARMs are androgen receptor ligands that band to the androgen receptor with differing sensitivities compared to that of testosterone. SARMs increase muscle power due to similar myoanabolic effects as testosterone.[64]

LGD-4033 is a nonsteroidal, orally active SARM. The phase I trial showed an increase in muscle mass in a short period, with no effect on fat mass.[65] Enobosarm (GTx-024) is an orally bioavailable non-steroidal SARM. The use of enobosarm led to significant improvements in lean body mass and physical function in a phase II, double-blind, placebo-controlled studies both in healthy elderly adults and in cancer patients. A phase III trial is ongoing.[66]

3) Growth hormone

Growth hormone (GH) enhances the release of liver-derived IGF-1. Several studies have shown that GH increased lean body mass.[67,68] However, using GH also led to a variety of side effects including muscle pain, edema, carpal tunnel syndrome and hyperglycemia.[69]

4) Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) binds androgen receptors and displays tissue-selective activation of androgenic signaling. Some studies have reported improved measures of muscle strength and physical function. However, overall, the benefit of DHEA on muscle strength and physical function in older adults remains inconclusive.[70]

5) Isoflavone

Six months of isoflavone supplementation increased fat-free mass and muscle mass index in postmenopausal women with sarcopenic obesity.[71]

2. Orexigenics

Ghrelin is a peptide hormone produced by the fundus of the stomach. It stimulates food intake and increases GH secretion. Because of its combined anabolic effects on skeletal muscle and appetite, ghrelin and low-molecular-weight agonists of the ghrelin receptor are considered attractive candidates for the treatment of sarcopenia.[72] Capromorelin, a ghrelin receptor agonist, increased lean body mass and stair climb in older patients with sarcopenia.[73] Ibutamoren (MK-0677), which also activates the ghrelin receptor to increase GH level, increased the ability to stair climb and decreased falls in persons with hip fracture within 24 weeks.[74] Anamorelin, a ghrelin agonist, improves lean body mass, performance status, and especially, quality of life in patients with cancer cachexia.[75]

Several hormones and peptides influence food intake by signaling in the hypothalamus. Melanocortin (MC) 4 receptor, which is expressed mainly in the paraventricular nucleus of the hypothalamus, is associated with anorexigenic signaling. Thus, inhibition of MC receptor activity

by infusion of an MC receptor antagonist or with the inverse agonist agouti-related protein results in increased food intake.[76,77] Megestrol acetate improves appetite and is associated with slight weight gain in patients with cancer, AIDS, and other underlying pathology.[78]

3. Cardiovascular Drugs

1) Angiotensin II-converting enzyme inhibitors

Angiotensin II-converting enzyme inhibitors may exert their beneficial effects on skeletal muscles through a number of different mechanisms.[79] Perindopril improved the distance walked in older persons and those with heart failure; it also decreased hip fracture.[80,81]

2) Adrenergic receptor antagonist

In a randomized, double-blind placebo-controlled phase II study of patients with lung or colorectal cancer, espindolol, a nonspecific β_1/β_2 adrenergic receptor antagonist, reversed body weight loss seen in the placebo group and maintained lean body mass. It also increased hand grip strength and showed trends in functional improvement.[82]

3) Statins (hydroxymethylglutaryl Co-A reductase inhibitors)

The beneficial effects of statins on skeletal muscle function might be explained by the reduced inflammation and vascular and metabolic effects associated with their use.[83]

4. Metabolic Agents

1) Creatine

Creatine plays an important role in protein metabolism and cellular metabolism. Creatine has been hypothesized to increase the expression of myogenic transcription factors such as myogenin and myogenic regulatory factor-4, which increases muscle mass and strength. Several studies of creatine supplementation have shown increased muscle strength and power. However, creatine supplementation may increase the risk of interstitial nephritis, highlighting the need for particular caution regarding its use in older people. Creatine is not currently recommended for sarcopenia.[79]

2) β-hydroxy-β-methylbutyrate

β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of the essential amino acid leucine that has been reported to have anabolic effects on protein metabolism. HMB stimulates protein synthesis via mTOR, a protein kinase that has a central role in controlling mRNA translation efficiency. HMB has been shown to affect muscle protein turnover by stimulating protein synthesis via the up-regulation of anabolic signaling pathways and by decreasing proteolysis via the down-regulation of catabolic signaling pathways.[84]

5. Myostatin Inhibition

Myostatin (GDF-8), a member of the TGF-β family, is produced in the skeletal muscle and prevents muscle growth and satellite cell production. It is exclusively expressed in skeletal muscle as a negative regulator of skeletal muscle growth. Active myostatin mostly binds to activin receptor IIB and engages the signaling cascade leading to the inhibition of myoblast differentiation and proliferation.[85,86] Therefore, agents which inhibit myostatin or block the activin receptor may be useful in increasing muscle mass.

REGN1033 (GDF8 antibody), a myostatin antagonist, and bimagrumab, an activin receptor inhibitor, are currently under development.[87]

6. Fast Skeletal Muscle Troponin Activator

Tirasemtiv sensitizes sarcomeres to calcium; this mechanism amplifies the muscle response to neuromuscular input, producing greater force with reduced nerve input. It significantly increases submaximal isometric force, forelimb grip strength, grid hang time, and rotarod performance in a female transgenic mouse model of amyotrophic lateral sclerosis (ALS).[88] Small studies have suggested the biological effects of tirasemtiv in patients with ALS, but a statistically significant signal was not observed in a large study.[89]

CK-2127107, a next-generation fast skeletal muscle troponin activator, has been shown to amplify the force-frequency muscle response in humans.[90]

7. Mitochondrial Function Enhancer

Elamipretide (Bendavia) has been shown to enhance adenosine triphosphate synthesis in multiple organs including the heart, kidneys, neurons, and skeletal muscle.[91]

8. Cell Therapy

Satellite cells, the adult skeletal muscle progenitor cells, have been considered the main cell type involved in skeletal muscle regeneration. However, other cell types, including mesoangioblasts, have recently been suggested to also participate in skeletal muscle regeneration.[92]

CONCLUSION

Sarcopenia is defined as the age-associated loss of muscle mass and function. Practically, the AWGS recommends an operational definition based on low muscle mass and low muscle function such as muscle strength and physical performance for the diagnosis of sarcopenia. This analysis can be done using DXA or BIA. Sarcopenia was recognized as an independent clinical condition in the ICD-10-CM. It was assigned code M62.84 and has been available in the United States since October 2016. The clinical consequences of sarcopenia are musculoskeletal (fall and fracture), cardiometabolic (diabetic mellitus, hypertension, dyslipidemia), and psychological (depression). However, its acceptance and awareness as a clinical entity have lagged. This may be due to the limitations of the current available effective therapy. No pharmacologic agent is as efficacious

as exercise and nutrition at present and there is an urgent need for new medication. Sarcopenia is the most important immediate clinical target in musculoskeletal science.

Conflicts of Interest Disclosures: The researcher claims no conflicts of interest.

REFERENCES

1. Rosenberg IH. Summary comments. Am J Clin Nutr 1989;50:1231-3.
2. Fearon K, Evans WJ, Anker SD. Myopenia-a new universal term for muscle wasting. J Cachexia Sarcopenia Muscle 2011;2:1-3.
3. Clark BC, Manini TM. Sarcopenia =/= dynapenia. J Gerontol A Biol Sci Med Sci 2008;63:829-34.
4. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 2011;12:403-9.
5. Correa-de-Araujo R, Hadley E. Skeletal muscle function deficit: a new terminology to embrace the evolving concepts of sarcopenia and age-related muscle dysfunction. J Gerontol A Biol Sci Med Sci 2014;69:591-4.
6. Anker SD, Coats AJ, Morley JE, Rosano G, Bernabei R, von Haehling S, et al. Muscle wasting disease: a proposal for a new disease classification. J Cachexia Sarcopenia Muscle 2014;5:1-3.
7. Cao L, Morley JE. Sarcopenia is recognized as an independent condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code. J Am Med Dir Assoc 2016;17:675-7.
8. Shefer G, Van de Mark DP, Richardson JB, Yablonka-Reuveni Z. Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle. Dev Biol 2006;294:50-66.
9. Verdijk LB, Koopman R, Schaart G, Meijer K, Savelberg HH, van Loon LJ. Satellite cell content is specifically reduced in type II skeletal muscle fibers in the elderly. Am J Physiol Endocrinol Metab 2007;292:E151-7.
10. Miljkovic N, Lim JY, Miljkovic I, Frontera WR. Aging of skeletal muscle fibers. Ann Rehabil Med 2015;39:155-62.
11. Lexell J. Human aging, muscle mass, and fiber type composition. J Gerontol A Biol Sci Med Sci 1995;50 Spec No:11-6.
12. Frontera WR, Suh D, Krivickas LS, Hughes VA, Goldstein R, Roubenoff R. Skeletal muscle fiber quality in older men and women. Am J Physiol Cell Physiol 2000;279:C611-8.
13. Ciciliot S, Rossi AC, Dyar KA, Blaauw B, Schiaffino S. Muscle type and fiber type specificity in muscle wasting. Int J Biochem Cell Biol 2013;45:2191-9.
14. Renganathan M, Messi ML, Delbono O. Dihydropyridine receptor-ryanodine receptor uncoupling in aged skeletal muscle. J Membr Biol 1997;157:247-53.
15. Manini TM, Clark BC. Dynapenia and aging: an update. J Gerontol A Biol Sci Med Sci 2012;67:28-40.
16. D'Antona G, Pellegrino MA, Adami R, Rossi R, Carlizzi CN, Canepari M, et al. The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. J Physiol 2003;552(Pt 2):499-511.
17. Ochala J, Frontera WR, Dorer DJ, Van Hoecke J, Krivickas LS. Single skeletal muscle fiber elastic and contractile characteristics in young and older men. J Gerontol A Biol Sci Med Sci 2007;62:375-81.
18. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol (1985) 2001;90:2157-65.
19. Broskey NT, Greggio C, Boss A, Boutant M, Dwyer A, Schlueter L, et al. Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training. J Clin Endocrinol Metab 2014;99:1852-61.
20. Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Sarcopenia in the elderly: diagnosis, physiopathology and treatment. Maturitas 2012;71:109-14.
21. Thomas DR. Adverse outcomes and functional consequences. Chichester (UK): John Wiley and Sons; 2012.
22. Zamboni M, Rossi AP, Zoico E. Sarcopenic obesity. Chichester (UK): John Wiley and Sons; 2012.
23. Kim NH, Kim HS, Eun CR, Seo JA, Cho HJ, Kim SG, et al. Depression is associated with sarcopenia, not central obesity, in elderly korean men. J Am Geriatr Soc 2011;59:2062-8.
24. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412-23.
25. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95-101.
26. McLean RR, Kiel DP. Developing consensus criteria for sarcopenia: an update. J Bone Miner Res 2015;30:588-92.
27. Kwon HJ, Ha YC, Park HM. The reference value of skeletal muscle mass index for defining the sarcopenia of women in Korea. J Bone Metab 2015;22:71-5.
28. Kim YS, Lee Y, Chung YS, Lee DJ, Joo NS, Hong D, et al. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the Fourth Korean National Health and Nutritional Examination Surveys. J Gerontol A Biol Sci Med Sci 2012;67:1107-13.
29. Kim TN, Yang SJ, Yoo HJ, Lim KI, Kang HJ, Song W, et al. Prevalence of sarcopenia and sarcopenic obesity in Korean adults: the Korean sarcopenic obesity study. Int J Obes (Lond) 2009;33:885-92.
30. Kwon HJ, Ha YC, Park HM. Prevalence of sarcopenia in the Korean woman based on the Korean National Health and Nutritional Examination Surveys. J Bone Metab 2016;23:23-6.
31. Lee ES, Park HM. Prevalence of sarcopenia in healthy Korean elderly women. J Bone Metab 2015;22:191-5.
32. Kalinkovich A, Livshits G. Sarcopenia: the search for emerging biomarkers. Ageing Res Rev 2015;22:58-71.
33. Tagliaferri C, Wittrant Y, Davicco MJ, Walrand S, Coxam V. Muscle and bone, two interconnected tissues. Ageing Res Rev 2015;21:55-70.
34. Gunton JE, Girgis CM, Baldock PA, Lips P. Bone muscle interactions and vitamin D. Bone 2015;80:89-94.
35. Hirschfeld HP, Kinsella R, Duque G. Osteosarcopenia: where bone, muscle, and fat collide. Osteoporos Int 2017;28:2781-90.

36. Huo YR, Suriyaarachchi P, Gomez F, Curcio CL, Boersma D, Gunawardene P, et al. Comprehensive nutritional status in sarcopenic-osteoporotic older fallers. J Nutr Health Aging 2015;19:474-80.
37. Sjöblom S, Suuronen J, Rikkonen T, Honkanen R, Kröger H, Sirola J. Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia. Maturitas 2013;75:175-80.
38. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care 2010;33:1652-4.
39. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm 2010;2010. pii: 289645.
40. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415-45.
41. Zoico E, Corzato F, Bambace C, Rossi AP, Micciolo R, Cinti S, et al. Myosteatosis and myofibrosis: relationship with aging, inflammation and insulin resistance. Arch Gerontol Geriatr 2013;57:411-6.
42. Ormsbee MJ, Prado CM, Ilich JZ, Purcell S, Siervo M, Folsom A, et al. Osteosarcopenic obesity: the role of bone, muscle, and fat on health. J Cachexia Sarcopenia Muscle 2014;5:183-92.
43. Ilich JZ, Kelly OJ, Inglis JE, Panton LB, Duque G, Ormsbee MJ. Interrelationship among muscle, fat, and bone: connecting the dots on cellular, hormonal, and whole body levels. Ageing Res Rev 2014;15:51-60.
44. Binkley N, Krueger D, Buehring B. What's in a name revisited: should osteoporosis and sarcopenia be considered components of "dysmobility syndrome?". Osteoporos Int 2013;24:2955-9.
45. Lee WJ, Liu LK, Hwang AC, Peng LN, Lin MH, Chen LK. Dysmobility syndrome and risk of mortality for community-dwelling middle-aged and older adults: the nexus of aging and body composition. Sci Rep 2017;7:8785.
46. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43:748-59.
47. Steffl M, Bohannon RW, Sontakova L, Tufano JJ, Shiells K, Holmerova I. Relationship between sarcopenia and physical activity in older people: a systematic review and meta-analysis. Clin Interv Aging 2017;12:835-845.
48. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation 2007;116:572-84.
49. Zembroń-Łacny A, Dziubek W, Rogowski Ł, Skorupka E, Dąbrowska G. Sarcopenia: monitoring, molecular mechanisms, and physical intervention. Physiol Res 2014;63:683-91.
50. Wolfe RR. Regulation of muscle protein by amino acids. J Nutr 2002;132:3219S-3224S.
51. Symons TB, Schutzler SE, Cocke TL, Chinkes DL, Wolfe RR, Paddon-Jones D. Aging does not impair the anabolic response to a protein-rich meal. Am J Clin Nutr 2007;86:451-6.
52. Calvani R, Miccheli A, Landi F, Bossola M, Cesari M, Leeuwenburgh C, et al. Current nutritional recommendations and novel dietary strategies to manage sarcopenia. J Frailty Aging 2013;2:38-53.
53. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14:542-59.
54. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33:929-36.
55. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care 2009;12:86-90.
56. Rizzoli R, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, et al. The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas 2014;79:122-32.
57. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013;24:23-57.
58. Rizzoli R, Boonen S, Brandi ML, Bruyère O, Cooper C, Kanis JA, et al. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 2013;29:305-13.
59. Lowe DA, Baltgalvis KA, Greising SM. Mechanisms behind estrogen's beneficial effect on muscle strength in females. Exerc Sport Sci Rev 2010;38:61-7.
60. Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Morley PM, Stauber PM, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 1997;46:410-3.
61. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev 1999;107:123-36.
62. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. J Gerontol A Biol Sci Med Sci 2003;58:618-25.
63. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Mac RP, Lee M, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 2005;90:678-88.
64. Mohler ML, Bohl CE, Jones A, Coss CC, Narayanan R, He Y, et al. Nonsteroidal selective androgen receptor modulators (SARMs): dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. J Med Chem 2009;52:3597-617.
65. Basaria S, Collins L, Dillon EL, Orwoll K, Storer TW, Miciek R, et al. The safety, pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men. J Gerontol A Biol Sci Med Sci 2013;68:87-95.
66. Crawford J, Prado CM, Johnston MA, Gralla RJ, Taylor RP, Han-

cock ML, et al. Study Design and Rationale for the Phase 3 Clinical Development Program of Enobosarm, a Selective Androgen Receptor Modulator, for the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER Trials). Curr Oncol Rep 2016;18:37.
67. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med 1990;323:1-6.
68. Kim MJ, Morley JE. The hormonal fountains of youth: myth or reality? J Endocrinol Invest 2005;28(11 Suppl Proceedings):5-14.
69. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 2007;146:104-15.
70. Baker WL, Karan S, Kenny AM. Effect of dehydroepiandrosterone on muscle strength and physical function in older adults: a systematic review. J Am Geriatr Soc 2011;59:997-1002.
71. Aubertin-Leheudre M, Lord C, Khalil A, Dionne IJ. Six months of isoflavone supplement increases fat-free mass in obese-sarcopenic postmenopausal women: a randomized double-blind controlled trial. Eur J Clin Nutr 2007;61:1442-4.
72. Wakabayashi H, Sakuma K. Comprehensive approach to sarcopenia treatment. Curr Clin Pharmacol 2014;9:171-80
73. White HK, Petrie CD, Landschulz W, MacLean D, Taylor A, Lyles K, et al. Effects of an oral growth hormone secretagogue in older adults. J Clin Endocrinol Metab 2009;94:1198-206.
74. Adunsky A, Chandler J, Heyden N, Lutkiewicz J, Scott BB, Berd Y, et al. MK-0677 (ibutamoren mesylate) for the treatment of patients recovering from hip fracture: a multicenter, randomized, placebo-controlled phase IIb study. Arch Gerontol Geriatr 2011;53:183-9.
75. Takayama K, Katakami N, Yokoyama T, Atagi S, Yoshimori K, Kagamu H, et al. Anamorelin (ONO-7643) in Japanese patients with non-small cell lung cancer and cachexia: results of a randomized phase 2 trial. Support Care Cancer 2016;24:3495-505.
76. Adan RA, Tiesjema B, Hillebrand JJ, la Fleur SE, Kas MJ, de Krom M. The MC4 receptor and control of appetite. Br J Pharmacol 2006;149:815-27.
77. Mosialou I, Shikhel S, Liu JM, Maurizi A, Luo N, He Z, et al. MC4R-dependent suppression of appetite by bone-derived lipocalin 2. Nature 2017;543:385-90.
78. Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Marti S. Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database Syst Rev 2013;(3):CD004310.
79. Burton LA, Sumukadas D. Optimal management of sarcopenia. Clin Interv Aging 2010;5:217-28.
80. Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo ME. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. Heart 2002;88:373-7.
81. Peters R, Beckett N, Burch L, de Vernejoul MC, Liu L, Duggan J, et al. The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). Age Ageing 2010;39:609-16.
82. Morley JE, von Haehling S, Anker SD. Are we closer to having drugs to treat muscle wasting disease? J Cachexia Sarcopenia Muscle 2014;5:83-7.
83. Lynch JE, Henderson NR, Ramage L, McMurdo ME, Witham MD. Association between statin medication use and improved outcomes during inpatient rehabilitation in older people. Age Ageing 2012;41:260-2.
84. Holeček M. Beta-hydroxy-beta-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions. J Cachexia Sarcopenia Muscle 2017;8:529-41.
85. Elkina Y, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: an overview. J Cachexia Sarcopenia Muscle 2011;2:143-151.
86. Kung T, Szabó T, Springer J, Doehner W, Anker SD, von Haehling S. Cachexia in heart disease: highlights from the ESC 2010. J Cachexia Sarcopenia Muscle 2011;2:63-9.
87. Morley JE. Pharmacologic options for the treatment of sarcopenia. Calcif Tissue Int 2016;98:319-33.
88. Hwee DT, Kennedy A, Ryans J, Russell AJ, Jia Z, Hinken AC, et al. Fast skeletal muscle troponin activator tirasemtiv increases muscle function and performance in the B6SJL-SOD1G93A ALS mouse model. PLoS One 2014;9:e96921.
89. Shefner JM, Wolff AA, Meng L, Bian A, Lee J, Barragan D, et al. A randomized, placebo-controlled, double-blind phase IIb trial evaluating the safety and efficacy of tirasemtiv in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2016;17:426-35.
90. Andrews JA, Miller TM, Vijayakumar V, Stoltz R, James JK, Meng L, et al. CK-2127107 amplifies skeletal muscle response to nerve activation in humans. Muscle Nerve 2018;57:729-34.
91. Sabbah HN, Gupta RC, Kohli S, Wang M, Hachem S, Zhang K. Chronic therapy with elamipretide (MTP-131), a novel mitochondria-targeting peptide, improves left ventricular and mitochondrial function in dogs with advanced heart failure. Circ Heart Fail 2016;9:e002206.
92. Sirabella D, De Angelis L, Berghella L. Sources for skeletal muscle repair: from satellite cells to reprogramming. J Cachexia Sarcopenia Muscle 2013;4:125-36.