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 krato-penia 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)

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

Table 1. Terms related to sarcopenia

| Loss of muscle | Reference |
|----------------|-----------|
| Age-related    | Rosenberg (1989) 1) |
| Mass           |           |
| Sarcopenia     |           |
| Strength       | Clark and Manini (2008) 3) |
| Dynapenia      |           |
| Kratopenia     | Morley et al. (2011) 6) |
| Age-/non-age-related | |
| Myopenia       | Fearon et al. (2011) 3) |
| Skeletal muscle function deficit | Correa-de-Araujo and Hardy (2014) 9) |
| 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 in-
cluding 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.13 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 ex-
plained by reductions in the intrinsic force-generating ca-
pacity 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.18

4) Excitation-contraction coupling

Aging causes a reduction in the number of dihydro-
pyridine 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 in-
stantaneous 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 in-
filtration 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 

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 es-
timated 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 de-
cade 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 

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          |

Sarcopenia in older populations is related to falls, func-
tional impairment, loss of independence, increased mortal-
ity, 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 ex-
penditure and may lead to weight gain and obesity. As a 
result, sarcopenia and obesity are associated with a wors-
ened 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 psychologi-
cal morbidities.

The negative health outcomes, including mobility limi-
tation, 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 im-
plications than a loss of muscle mass and these 2 condi-
tions should be considered independently.24

The nervous system also contributes to increased or de-
creased muscle strength. Both neurological and muscular 

CLINICAL CONSEQUENCES

Moreover, increased obesity, 

Table 2. Changes in muscle mass and strength with age based on 
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| Age (yr) | Loss of muscle mass | Loss of muscle strength |
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| Until 70 | 8%/decade           | 10%–15%/decade          |
| After 70 | 15%/decade          | 25%–40%/decade          |

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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). The suggested cutoff values are 7.26 kg/m² in men and 5.5 kg/m² 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/m² in men and 5.4 kg/m² in women by DXA. By bioimpedance analysis (BIA), the suggested cutoffs are 7.0 kg/m² in men and 5.7 kg/m² 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

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/m² and the cutoff of 4.4 kg/m² 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 3. Cutoffs for the diagnosis of sarcopenia**

| Variable                          | EWGSOP | AWGS |
|----------------------------------|--------|------|
| Skeletal muscle index (kg/m²)    |        |      |
| 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.

**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.
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.23

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.24

**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.25

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.31,32

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.51 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.
years.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{60}

**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.\textsuperscript{61,62} Testosterone not only increases muscle mass and power but also decreases fat mass in elderly men.\textsuperscript{63,64} 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 bind to the androgen receptor with differing sensitivities compared to that of testosterone. SARMs increase muscle power due to similar myoanabolic effects as testosterone.\textsuperscript{65}

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.\textsuperscript{66} 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.\textsuperscript{67}

3) Growth hormone

Growth hormone (GH) enhances the release of liver-derived IGF-1. Several studies have shown that GH increased lean body mass.\textsuperscript{68,69} However, using GH also led to a variety of side effects including muscle pain, edema, carpal tunnel syndrome and hyperglycemia.\textsuperscript{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.\textsuperscript{70}

5) Isoflavone

Six months of isoflavone supplementation increased fat-free mass and muscle mass index in postmenopausal women with sarcopenic obesity.\textsuperscript{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.\textsuperscript{72} Capromorelin, a ghrelin receptor agonist, increased lean body mass and stair climb in older patients with sarcopenia.\textsuperscript{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.\textsuperscript{74} Anamorelin, a ghrelin agonist, improves lean body mass, performance status, and especially, quality of life in patients with cancer cachexia.\textsuperscript{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.\textsuperscript{76,77} Megestrol acetate improves appetite and is associated with slight weight gain in patients with cancer, AIDS, and other underlying pathology.\textsuperscript{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.\textsuperscript{79} Perindopril improved the distance walked in older persons and those with heart failure; it also decreased hip fracture.\textsuperscript{80,81}

2) Adrenergic receptor antagonist

In a randomized, double-blind placebo-controlled phase II study of patients with lung or colorectal cancer, espinolol, a nonspecific β₁/β₂ 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{89}

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