**Sarcopenia**

Cai Junxiang1, Lou Hui-ling2

1 Department of Geriatrics, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China.

2 Department of Geriatrics, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China.

Correspondence

Lou Hui-ling, Department of Geriatrics, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China.

Email: huilinglou@163.com

Fund Information: Guangzhou Health and Family Planning Commission General Guidance Fund, Grant/Award Number: 20181A011008;

Corresponding author: Lou Huiling, Department of Geriatrics, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China. E-mail: [huilinglou@163.com](mailto:huilinglou@163.com)

**Abstract：**

Sarcopenia is a syndrome associated with low muscle mass, muscle strength and physical performance. The morbidity rate of sarcopenia is pretty high in elderly people who are lake of physical activity, chronic disease patients and patients with malignancy. Patients have higher risks of falling, frailty and disability, and are more likely to be independence. Sarcopenia also impact on the quality of life and clinical outcome directly, and if we pay enough attention to sarcopenia early in life，it can help us delaying frailty. Sarcopenia are categorized as aged-related sarcopenia, sarcopenia with malnutrition, sarcopenia associated with activity, disease-related sarcopenia. Aging, endocrine changes, chronic inflammation, cachexia, malnutrition, vitamin D deficiency can lead to sarcopenia. The European Working Group on Sarcopenia in Older People revises their consensus recently, and recommends using muscle strength as the most important parameter of sarcopenia, and they updates its algorithm for sarcopenia case-finding，diagnosis and severity determination. Mechanism of sarcopenia has been realized within more and more studies developing. Nutrition supplement, resistance exercise and hormone replacement therapy can improve muscle mass and strength, delay function decline, improve quality of life. Etiology of sarcopenia is not integral yet, pharmacotherapy still needs more powerful evidence.

**Key words：**sarcopenia, aging, cachexia, nutrition , inflammation.

1. Introduction

Sarcopenia is known as age-related disease. It is a degenerative disease that occurs with increasing age, which is characterized by loss of skeletal muscle mass，muscle strength and dysfunction [1]. Except for age, various factors such as skeletal muscle cell denervation, mitophagy, inflammation, nutritional absorption and utilization disorders, disuse, obesity, fat infiltration and endocrine changes can waste skeletal muscle and can cause sarcopenia [2], patients have had less muscle strength, were easy to get fractures, insulin resistance, and dependent living ability [3].

Sarcopenia is common in the elderly, chronic diseases, frailty and cachexia which is associated with dysfunction, increasing hospitalization, nosocomial infction, and reduced survival rate. The pathophysiological mechanism is that patients with sarcopenia have smaller，fewer skeletal muscle cells volume (the number of muscle cells per unit area increases), and the decrease in the number of fast-twitch fibers is partially transformed into slow-twitch fibers (type IIa and type I cells), which ultimately leads to a decrease in skeletal muscle strength. Function is reduced [[4, 5]]. The main clinical symptoms are fatigue, weakness, falls, disability, and disability, which are closely related to the clinical outcome of the patient [6].

Regarding the definition of sarcopenia, the consensus of the European Working Group on Sarcopenia is widely used internationally. The European Working Group on Sarcopenia in Older People2 (EWGSOP2) updated the European consensus in 2018. [7]: Sarcopenia is a syndrome characterized by low muscle strength (low muscle strength), low muscle quantity and quality (low muscle quantity and quality), and low physical performance (low physical performance). Lead to disability, low quality of life and death; this update emphasizes low muscle strength as a key feature of sarcopenia. Compared with low muscle mass, low muscle strength is a more significant determinant of sarcopenia and is more effective. To predict adverse outcomes, it is recommended to use low muscle strength as the most important parameter of sarcopenia.

Due to differences in race, genetic background, and body type, the Asian Working Group for Sarcopenia (AWGS) also proposed the Asian Sarcopenia consensus in 2014 [8] and updated it in 2016 [ 9] and was updated again in 2019, and for the first time it was proposed to measure calf circumference, SARC-F and SARC-CalF as one of the screening criteria for sarcopenia, and the diagnostic criteria for sarcopenia should be determined by male grip strength< 26kg, female grip strength <18kg adjusted to male grip strength <28kg, female grip strength <18kg, and the concept of "possible sarcopenia patients" is also introduced. In primary care and preventive health care institutions, low muscle mass +/- physical fitness reduce. In 2016, sarcopenia was also officially included in the ICD disease code, indicating that sarcopenia, as a disease with its unique characteristics, will be widely valued by the medical community, and the understanding of screening, diagnosis, intervention and treatment of the disease will be more precise[10].

classification

According to the pathological classification, sarcopenia can be divided into two types: physiological and pathological. Pathological is divided into benign and malignant, which are caused by benign diseases and malignant tumors. Physiological includes age-related sarcopenia [10]; Sarcopenia caused by tumors is mostly caused by muscle loss caused by cachexia. Cachexia is a metabolic syndrome related to the primary disease, with significant muscle loss, with or without fat loss [11].

Pathogenesis

Human muscles have physiological changes with age, reaching the highest peak of structure and function at the age of 20 to 40. The quality and quantity of muscles in people aged 40 to 60 begin to decrease, and the body accelerates the storage of fat. Insulin resistance problems. For people aged 60 to 70, as hormone changes bring about problems such as changes in muscle and fat distribution, with age, other organ functions decline, nutrient intake, absorption, and digestion function decrease, which increases the risk of muscle loss. Because of the effects of aging and other aspects, people over 70 years old, even if they exercise properly, the ability of muscles to increase protein synthesis will be reduced. Therefore, early attention to people at high risk of sarcopenia can effectively prevent muscle loss and delay aging. The EWGSOP epidemiological survey shows that the prevalence of sarcopenia is 5%-13% in the elderly aged 60-70 years, and the prevalence rate is 11%-50% among the elderly over 80 years old [10]; AWGS pointed out that the prevalence of sarcopenia is between 5.5% and 25.7% in the Asian Sarcopenia Diagnosis and Treatment Consensus, which was updated in 2019, with males accounting for the majority (5.1%-21.0% for males and 4.1% for females) -16.3%. With the progress of research, people have a clearer understanding of the mechanism of sarcopenia, providing a basis for early prevention and treatment.

3.1 Sarcopenia and age

Skeletal muscle is the largest protein store in the human body, accounting for 60% of the total protein in the human body. Protein weight is about 20% of muscle weight. As age increases, protein synthesis reaction decreases and decomposition increases, which is one of the key factors causing age-related sarcopenia.

As age increases, motor neurons will also undergo corresponding degenerative changes, DNA damage and genotoxic stress accumulate, destroy the structural and functional integrity of the neuromuscular junction (neuromuscular junction), resulting in denervation of skeletal muscle fibers. , Skeletal muscle fibers will also be damaged following aging, which may also be an important cause of aging skeletal muscle function decline 12-14].

Studies have found that skeletal muscle mitochondrial dysfunction and autophagy programmed death of skeletal muscle are the main causes of aging. The loss of mtDNA histones and proofreading system Forkhead transcription factor 3 (Forkhead box O3, FOXO3) has been proven to control muscle autonomy. The key factor of phagocytosis [15, 16]; phosphatidylinositol kinase 3-protein kinase B-mammalian target of rapamycin (phosphatidylinositol-3-kinase/protein kinase B/the mammalian target of Rapamycin, PI3K- The AKT-mTOR) channel regulates muscle protein synthesis [11]. With age, the rate of mitochondrial protein synthesis and skeletal muscle heavy chain protein synthesis reduces protein synthesis; various growth factors, insulin receptors, inflammatory factors, etc. Extracellular signal molecules bind to protein G and couple to tyrosine kinase receptors, activate PI3K (phosphatidylinositol-3-kinase) downstream of the pathway, and affect protein synthesis; lack of physical activity in the elderly increases autophagy activity and activity Oxygen cluster (reactive oxy gen species, ROS) content will also be moderately increased, through the mitogen-activated protein kinase (mitogen-activated protein kinase, MAPK) pathway and other signal transduction pathways, the energy metabolism of ATP enzyme, cytochrome The expression of some enzymes such as C oxidase is reduced, which accelerates the decomposition of skeletal muscle protein and reduces protein synthesis; and exercise can activate the above pathways to resist excessive increase in ROS and resist autophagy [17].

3.2 Sarcopenia and endocrine

A variety of endocrine hormones such as growth hormone and androgen participate in the regulation of human skeletal muscle metabolism and protein synthesis. Growth hormone, testosterone, and insulin-like growth factors have a clear correlation with muscle mass, muscle strength and grip strength. Growth hormone (GH) can not only enhance muscle anabolism, increase muscle mass, but also improve muscle strength and grip strength of elderly individuals. Giovannini.S [18] et al. used growth hormone replacement therapy to remove the pituitary in rats, which restored the muscle mass and improved the size of muscle fibers; T. Brioche [19] et al. found that small doses The use of GH can effectively prevent age-related muscle mass loss. Salomon. F[20] treatment of elderly men with GH increases the plasma concentration of insulin-like growth factors -1 (IGF-1) in the body And lean body mass, while reducing body fat. However, other negative metabolic effects brought by GH have restricted the current clinical use of growth hormone.

Testosterone is currently recognized as an endocrine hormone that significantly improves muscle mass, grip strength, and muscle strength. It stimulates β-catenin connexin to increase the proliferation of astrocytes. With age, the content of testosterone in the body decreases [21], and due to the increase of sex hormone-binding globulin (SHBG), the bioavailability of free testosterone or testosterone decreases more significantly, which has a significant effect on muscles. The protective effect decreased more obviously. Baumgartner. RN[22] et al. found that male hormones play an important role in the regulation of sarcopenia. Muscle mass, energy intake, physical activity, grip strength, IGF-1 levels were significantly positively correlated with free testosterone, and significantly negatively correlated with SHBG. The testosterone replacement therapy showed that the muscle mass and strength of the experimental subjects increased significantly, and there was no significant decrease in body fat [23]. Replacement therapy with androgens has certain prospects for the prevention and treatment of sarcopenia in the future, but there are still safety issues such as the applicable population and the lowest effective dose.

The role of estrogen in muscle mass, muscle strength and function is still controversial. Virginie Messier[24] and others believe that the sharp drop in estrogen levels in the 3-5 years after menopause may also play a role in the loss of muscle mass. The potential effects are specifically manifested as a decrease in the number of type II muscle fibers and motor units, and an increase in intramuscular fat. In addition, Sorensen MB[25] found in a placebo-controlled crossover experiment that the lean body mass and bone mineral density (BMD) of the population during hormone replacement therapy (HRT) increased, and the fat mass decreased. . But on the contrary, there are also a number of cross-sectional studies of elderly women studying HRT that HRT has nothing to do with lean body mass or strength, and estrogen has nothing to do with female muscle mass or strength [26-28]. Kenny AM [29] et al. found that there was no difference in the prevalence of sarcopenia between women taking HRT and not using HRT. The role of estrogen in age-related sarcopenia is still a hot topic.

Insulin-like growth factor (IGF-1) plays an important role in the regulation of human development, and has a clear correlation with muscle mass, muscle strength and grip strength, and has a good anabolic effect on muscle tissue [30]. Overexpression of IGF-1 in muscles can combat age-related sarcopenia. IGF-1 binds to the receptor to regulate the downstream PI3K/AKT system, and the IGF-1/PI3K/Akt pathway has been defined to be responsible for mediating protein synthesis pathways [17, 31, 32].

Insulin resistance is also one of the important pathogenesis of sarcopenia. Skeletal muscle is the main part of the body’s postprandial glucose processing. Therefore, insulin resistance (IR) in this tissue can lead to severe systemic metabolic disorders [33]. In muscle, insulin plays a major role in inhibiting protein catabolism. The role, insulin-mediated hyperplasia of muscle mass, has been attributed to the activation of p38 protein and mammalian target rapamycin (mTOR)/p70S6 kinase, which stimulates mRNA translation [34]. The role of insulin resistance in the human body is most likely to be regulated by increasing perfusion to enhance the utilization of amino acids, leading to muscle damage in the elderly. Preethi Srikanthan [35] et al. found that skeletal muscle mass and body weight are negatively correlated with insulin resistance.

In addition, abnormal thyroid function is also one of the pathogenesis of sarcopenia[11]. Some studies believe that hypothyroidism and hyperthyroidism will affect the quality and strength of limb muscles, but there is also scholar Min Kyong Moon[36] et al. found that subclinical hypothyroidism has little effect on muscle quality and quantity, and it is possible that subclinical hypothyroidism has nothing to do with the occurrence of sarcopenia.

3.3 Sarcopenia and inflammation

Low-grade chronic inflammation is considered to be a potential molecular mechanism of aging and age-related diseases, and it can serve as a bridge between normal aging and age-related physiological and pathological processes [32]. Inflammation is related to oxidative damage, activating the ubiquitin-protease system to promote protein degradation, causing age-related decline in muscle mass and strength. The level of key factors of inflammation, such as interleukin-1β (Interleukin-1β, IL-1β), tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2 (Cyclooxygenase-2, COX-2) ) And interleukin-6 (Interleukin-6, IL-6), both have been proven to be up-regulated during the aging process. By activating NF-κB, it generates apoptosis signals such as capasase8 [17] and up-regulates ubiquitin genes. Affect the cell cycle of skeletal muscle, skeletal muscle protein degradation and mediate inflammation [37]. In a study of the elderly in the Netherlands, high levels of IL-6 and C-reactive protein (CRP) increase the risk of muscle mass and muscle strength loss [38]. The process of oxidative stress also promotes the inflammatory response of skeletal muscle cells, and reactive oxygen species (ROS), as a second messenger, directly or indirectly affects NF-κB, leading to increased skeletal muscle cell decomposition and decreased protein synthesis [32].

3.4 Sarcopenia and cachexia

Regardless of the underlying disease, the reduction of skeletal muscle mass is considered to be the most clinically relevant phenotypic feature of cancer cachexia. Tumor patients have insufficient nutritional intake due to the characteristics of tumor cell metabolism, the influence of antitumor therapy, psychophysiological factors, immune inflammatory cytokines, etc. [39], tumors rely on the human body to grow and are consumed during the development of tumors With limited protein and energy in the body, the breakdown of muscle protein is greatly increased. This is due to the unique metabolic characteristics of tumors.

In terms of metabolism, tumor cells can perform glycolysis (Warburg effect) on a large amount of ingested glucose, which not only provides energy for tumor cells, but also provides them with reduced coenzyme II (nicotinamide adenine dinucleotide phosphate, NADPH), ribose And some non-essential amino acids and other biosynthetic raw materials to meet the needs of its rapid growth.

In addition to glycolysis, tumor cells also obtain a large amount of nitrogen sources such as glutamine through the tricarboxylic acid cycle. Even if the body's intake of energy and protein is insufficient or the protein synthesis process is reduced, tumors can use protein in preference to other tissues and degrade part of the skeletal muscle protein to maintain the energy and protein needs of tumor growth. Under cachexia conditions, actomyosin, actin, and myosin will be selectively decomposed, and the expression of myosin will also be reduced. The second is the decrease in protein synthesis. Tumors also promote the development of sarcopenia by affecting the expression of inflammatory factors. During tumor growth, it up-regulates the expression of TNF-α, activates NF-κB, and promotes iNOS protein synthesis. The downstream product of iNOS increases the synthesis of nitric oxide (NO), and many of the factors that can induce muscle reduction NO-dependent approach [17]. In addition to protein changes, the degradation of muscle cell DNA under tumor conditions also accelerates, leading to an increase in the number of apoptotic muscle cells.

Cachexia is the main cause of sarcopenia caused by tumors and is related to wasting disease states such as cancer and end-stage renal disease. Most patients with cachexia have sarcopenia, but most patients with sarcopenia do not necessarily have cachexia.

3.5 Sarcopenia and intestinal bacteria

Intestinal flora is a hot topic in current research. There are tens of billions of bacteria in the intestine. As an independent "organ", it affects the body's metabolism, endocrine, and immune function changes. The stability of the intestinal microecology plays an important role in the aging process. Intestinal flora can enhance host health and delay aging, improve immune homeostasis, prevent insulin resistance, and inhibit chronic inflammation by improving antioxidant activity, inhibiting inflammatory factors and inflammatory cells.[40]

Changes in the intestinal flora are obviously related to changes in muscle state caused by aging. Jay Siddharth [41] and others studied the gut microbiota and muscle physiology of aged rats. The experimental results showed that aging changes the composition of intestinal microbes, and aging has the potential to change the metabolism of intestinal bacteria. The age-related changes of intestinal microbes and the physiological decrease of musculoskeletal function are related to the inflammatory state and immune state of aged adult rats.

Laure B. Bindels [42] and others found that in the treatment of sarcopenia mice caused by leukemia, probiotic supplementation can interact with host tissues to control inflammation and induce changes in muscle atrophy markers. After oral supplementation of Leukemia-sarcopenia model mice with Lactobacillus reuteri 100-23 and Lactobacillus gasseri 311476, the weight of the tibialis muscle of the mice increased, and the levels of IL-4 and IL-6 in serum were higher than before supplementation. The expression of gastrocnemius and tibial muscle atrophy markers Atrogin-1, MuRF1, etc., decreased to varying degrees. Maintaining the steady state of the intestinal flora by supplementing probiotics and other means may bring new hope for the treatment of sarcopenia.

3.6 Sarcopenia and Vitamin D

Vitamin D is involved in the maintenance of muscle strength and strength. Vitamin D deficiency may affect muscle protein turnover by inducing hypocalcemia and reducing insulin secretion. In a study on the effect of vitamin D and leucine-rich whey protein nutritional supplements on elderly sarcopenia measures, a 13-week oral nutritional supplement of vitamin D and leucine-rich whey protein The supplementation of medicine can improve the muscle mass and lower limb function of the elderly [43]. A variety of vitamin D metabolites also affect muscle cell metabolism in various forms: 1,25-dihydroxyvitamin D3[1,25-(OH)2D3] One of the targets of action is muscle cells, severely 1,25 The clinical symptoms of (OH)2D3 deficiency (<25nmol/L) are related to myopathy, muscle pain and gait disturbance [44]. Lower 25-dihydroxyvitamin D (25-OHD) and higher parathyroid hormone (PTH) levels increase the risk of sarcopenia in the elderly [45].

3.7 Sarcopenia and nutrition

Malnutrition is a common senile syndrome and is closely related to the adverse outcomes of elderly hospitalized patients. Nutrients such as protein play an important role in maintaining muscle mass and muscle function in patients with malnutrition.

Whey protein is a high-quality animal protein with high digestibility and utilization rate. It contains a large amount of branched-chain amino acids that are beneficial to the balance of muscle protein. The composition of amino acids is similar to the essential amino acid requirements of the human body. It can promote muscle protein synthesis and prevent sarcopenia. Important role [46-48].

Leucine has a promoting effect on muscle anabolism and can stimulate protein synthesis through the signal pathway of mammalian rapamycin complex 1, effectively stimulating the release of IGF-1. Leucine activates the mammalian target of rapamycin (mTOR) and eukaryotic initiation factor (eIF) to stimulate muscle protein synthesis, which is 10 times that of other amino acids and phosphorylates FOXO and phosphorylates The later FOXO is inactivated to prevent the ubiquitination-protease pathway from decomposing proteins to inhibit muscle atrophy [49].

In addition, the minerals magnesium, selenium and calcium may also be nutrients for the prevention and treatment of sarcopenia [50].

Four, diagnosis

4.1 Diagnosis

The EWGSOP2, which was updated in 2018, updated the new diagnosis process for sarcopenia: Finding Cases-Evaluation-Confirmation-Severity.

First, through the SARC-F questionnaire or the Ishii screening test in Japan, the suspected sarcopenia cases were found, namely, from strength (Strength), walking (Assistance in walk), getting up (Rise from chair), climbing stairs (Climb stairs), falling ( Fall) Five aspects are used to assess the condition of the muscles from the subject’s own feelings, and screen out people at high risk of sarcopenia. Among them, it is believed that SARC-F is also applicable to the Chinese population [7]. Those with a total score greater than 4 are diagnosed as sarcopenia

By measuring grip strength and sitting time to assess muscle strength, abnormal persons can be diagnosed by detecting muscle mass. Further testing for pace, simple physical performance test (the Short Physical Performance Battery, SPPB), timed-up and go test (the Timed-Up and Go test, TUG), 400-meter walk test, etc. to judge the body function, assess the severity of sarcopenia degree.

4.2 Methods for clinical testing of muscle mass:

Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standards for detecting muscle mass, and dualenergy X-ray absorptiometry (DXA) is the first two The preferred alternative method, bioimpedance is used to detect the amount of fat and lean body mass, and the detection instrument is lighter than DXA.

4.2.1 Detection of skeletal muscle mass:

(1) Dual-energy X-ray absorption spectroscopy and bioimpedance analysis (BIA) can be used to measure the appendicular skeletal muscle (ASM) of the extremities, with height correction, and the relative skeletal muscle mass index to reflect muscle mass Characterization of loss: ASM/height 2 = skeletal muscle mass of limbs (kg)/height (m) 2, ASM/height 2 is the most widely used parameter for judging sarcopenia; different countries have different races The cut-off points for the diagnosis of sarcopenia muscle mass are also inconsistent. The diagnostic criteria of the European Working Group on Sarcopenia: When the ASM/height2 value is lower than the ASM/height2 value of the young control group, 2×SD Above, under specific circumstances, EWGSOP2 recommends using -2.5 standard deviations for a more conservative diagnosis: skeletal muscle mass (ASM)/height of the limbs 2: male <7.0kg/m2, female <6.0kg/m2 Sarcopenia can be diagnosed [7]. my country is currently basically using European standards. (3) Three-dimensional imaging techniques such as CT and MRI can also measure skeletal muscle mass, mainly measuring the cross-sectional area (CSA) of the L3 plane and the mid-thigh muscle.

4.2.2 Detection of muscle strength: Grip strength detection can be used, which is convenient for clinical use. It is often used to measure the dominant hand grip strength: male grip strength <27kg, female grip strength <16kg; it can also be used to measure the muscle strength of the lower limbs by measuring 5 sitting and standing tests.

4.3 The diagnostic process of sarcopenia of the Asian Sarcopenia Working Group (see Figure 2)

Figure 2 The diagnostic pathway of sarcopenia in the Asian Sarcopenia Working Group

Five, treatment

At present, the mechanism of sarcopenia still needs to be studied in depth, mainly involving aging and decline of neuromuscular function, decreased exercise volume and increased active oxygen levels, decreased protein intake and muscle-specific protein synthesis, increased body fat and visceral fat, chronic inflammation, and adverse effects The skeletal muscle mitochondrial function, hormone level changes, oxidative damage, apoptosis and microenvironment, autophagy, etc. Therefore, the intervention of sarcopenia and the treatment progress in recent years are mainly manifested in the following aspects.

5.1 Nutrition therapy

Nutritional therapy is one of the most important ways to interfere with sarcopenia, and the quality and quantity of protein intake are the key. Increasing the body's intake of protein and amino acids has a certain effect on the prevention and treatment of sarcopenia.

5.1.1 Protein supplement

The recommended dietary allowance (RDA) of 1.0—1.5g/kg/d helps maintain nitrogen balance and may reduce the reduction of protein synthesis function caused by the reduction of energy supply. D'Souza RF [51] et al. conducted a study on 46 elderly males. After resistance exercise (RE), immediately after taking a non-energy drink (placebo) or a drink containing whey protein, the muscles contained Leucine and whey protein intake are significantly positively correlated (r=0.51, P＜0.001; r=0.32, P=0.026); it shows that dietary protein intake is directly proportional to the amount of muscle protein.

When supplementing protein in the diet, pay particular attention to the digestibility and utilization of amino acids. Divide protein into multiple portions a day instead of one-time large amounts of protein. Increase the content of essential amino acids, especially leucine, within a reasonable range. Pay attention to matching with other types of foods such as carbohydrates [52]. Burd NA[53] and others asked healthy elderly male researchers to take one group of 20g whey protein and the other group to take the same amount of casein, the concentration of branched chain amino acid (BCAA) and leucine in the two groups Both were significantly increased, and the peak appeared 60 minutes after oral administration, but the phenomenon was even more pronounced for researchers taking the whey protein group. Both whey protein and casein can promote protein synthesis, but whey protein is better than casein;

Intake of high-quality protein after exercise is more conducive to muscle protein synthesis, absorption and utilization. It is recommended after 3 meals [54]. Supplementing whey protein twice can significantly improve muscle mass within 30-40 minutes after exercise.

In the elderly, ensuring the balance between daily dietary intake and energy requirements is also an important treatment to prevent muscle protein consumption and breakdown. For patients with insufficient intake, oral nutritional supplements (ONS) can be used.

5.1.2 Vitamin D

Studies have shown that the risk of sarcopenia in people with low serum 25-hydroxyvitamin D (<25 nmoL/L) is 2.14 times that of people with high levels (>50 nmoL/L). People with high levels of parathyroid hormone (≤4.0 pmoL/L) are less than those with low levels of parathyroid hormone <4. O pmoL/L) are more likely to suffer from sarcopenia. Supplement 800 Iu of vitamin D daily. After 2-12 months, the muscle strength of the lower limbs can be significantly increased; vitamin D supplementation can improve muscle protein synthesis and muscle strength, but whether it can improve muscle function still needs further research.

5.1.3 Some nutrients with special functions

Studies have also shown that omega-3 fatty acid supplements, ɑ-linolenic acid supplements, etc. can affect cell signaling pathways, activate transcription factors, etc., and promote the synthesis of skeletal muscle protein. Antioxidant and anti-inflammatory can be used for early prevention of sarcopenia[55].

5.2 Exercise therapy

Studies have found that long-term lack of physical exercise and sedentary behavior will lead to a decrease in protein intake during muscle synthesis. Long-term bed rest, limited activity, and lack of physical activity will accelerate muscle atrophy in the elderly and cachexia patients, resulting in sarcopenia. These patients have more restricted physical activity after suffering from sarcopenia, and the impairment of muscle strength and function increases, resulting in a vicious circle. Exercise therapy is another important preventive and treatment method for intervention in sarcopenia [56]. Exercise reduces or delays the decline in muscle regeneration, increases satellite cells and enhances their activation, and reduces fibrosis formation. Exercise can also reduce age-related intermuscular fat accumulation and change intramuscular lipids (IMCLs), improve the contractile function of muscle cells and tissues, and improve impaired muscle metabolism including insulin resistance and mitochondrial dysfunction. The types of exercise therapy are divided into aerobic exercise, muscle strength improvement, body balance and coordination training.

Resistance exercise (RE) is one of the best non-drug treatments for combating sarcopenia recommended by major guidelines. It strengthens muscle strength, muscle strength and physical fitness, thereby improving and improving the quality of life[57]]. A 12-week knee resistance training for 11 elderly people (134%; P <0.05) showed a significant increase in skeletal muscle mass. Exercise can profoundly improve muscle metabolism, strength and function [58]. Regular resistance training can increase lean body mass, reduce fat content, and reduce muscle mass loss [59].

5.3 Hormone therapy

For sarcopenia patients, exercise, nutritional therapy or additional oral nutritional supplements are important measures for early prevention and intervention. For patients with severe sarcopenia, especially sarcopenia caused by tumors, early treatment with drugs can greatly improve the prognosis of the disease.

Hormones can regulate the structure and function of muscle protein. Decreased levels of androgens, growth hormone, and IGF-1, increased levels of glucocorticoids, protein production [60] Testosterone or growth hormone can increase muscle mass, maintain lean body mass except fat, and also have a certain effect on increasing muscle strength . Hormonal drugs such as androgens are in clinical trials, and selective androgen receptor modulators have also entered clinical use abroad. Growth hormone secretagogue receptors, anti-myostatin analogues, nanometer megestrol acetate, etc. are undergoing trials, but whether they can play a role in the treatment of sarcopenia in the clinic is worthy of further research.

5.4 Other

Creatine is an organic acid containing nitrogen. It exists in muscles and can be synthesized by the human body or obtained from food. Creatine can promote the rapid synthesis of ATP to provide energy required for exercise during human exercise, can promote the increase of osmotic pressure in muscle cells, and induce myogenic transcription factors such as myogenin and MRF-4 (myogenic The expression of regulatory factor-4) changes the transcription level of tRNA that regulates muscle cell protein synthesis, increases muscle mass and muscle strength [61], and regulates muscle protein synthesis[62]. However, taking large amounts of creatine for a long time can cause side effects such as muscle cramps, gastrointestinal diseases, and may cause interstitial nephritis, so elderly patients should be used with caution.

Β2 adrenergic receptor agonists such as formoterol and salmeterol can promote protein synthesis, inhibit its decomposition, and reduce fat content. It can also promote skeletal muscle growth by inhibiting the expression of myostatin and increase muscle growth. The mass and muscle strength of the rat soleus muscle. The macrolide antibiotic roxithromycin (RM) also has the effect of improving the state of muscle atrophy. It can also increase the weight of skeletal muscle in a mouse model of tumor cachexia by reducing the level of cytokines and inhibiting aseptic inflammation [63 ].

Metabolic changes are one of the important causes of tumor-related cachexia. Anti-catabolism based on this mechanism to improve tumor-induced sarcopenia is a hot research topic recently. The currently recommended drugs include fish oil, branched-chain amino acids, cytokine antagonists, non-steroidal anti-inflammatory drugs, and metabolic cofactors, which are still in clinical trials. Except for thalidomide, none of the above-mentioned drugs have significant efficacy. Significantly improve the clinical outcome of patients with tumor cachexia.

The new molecular targeted therapies being studied also bring new prospects for the treatment of sarcopenia. Serum and glucocorticoid induced kinase 1 (serum and glucocorticoid induced kinase 1, SGK1) reduce proteolysis and autophagy, and enhance protein synthesis; ciliary neurotrophic factor agonists enhance motor neuron endplate function; auxiliary activator 1α (peroxisome Proliferators activated receptor gamma co-activator 1 alpha, PGC1α) agonist stimulates mitochondrial biosynthesis [64]; recombinant human CDGSH iron sulfur domain (CisD) protein replacement can improve the permeability of the outer mitochondrial membrane[65]; Even nitric oxide (isosorbide dinitrate) increases muscle blood flow, biguanides [66] increases nitric oxide function, inhibits the translocation of BAX to the mitochondrial membrane, angiotensin converting enzyme inhibitors [67] (angiotensin converting enzyme inhibitors, ACEI)/angiotensin receptor blocker [68](angiotensin Receptor Blocker, ARB) can improve skeletal muscle remodeling and inhibit disuse skeletal muscle apoptosis. Increase lean body tissue by changing body fat distribution and so on.

Outlook

With the advent of the "silver hair" wave, sarcopenia seriously endangers the health and quality of life of the elderly, and causes serious economic and social burdens on the family and society, which must arouse great attention. At present, the mechanism of sarcopenia is not very clear. The treatment mainly depends on nutrition and resistance exercise. There is still a lack of strong evidence in drug treatment. Actively carry out research on the mechanism of sarcopenia, and actively carry out early screening and prevention and treatment to delay the treatment. Preventing muscle loss, improving muscle mass and strength, and improving the quality of life and body functions have great social significance for healthy China.

**references**

[1] Rosenberg I H. Sarcopenia: Origins and clinical relevance. J Nutr. 1997;127(5 Suppl):990S-991S.

[2] Han A, Bokshan SL, Marcaccio SE, et al. Diagnostic criteria and clinical outcomes in sarcopenia research: A literature review. J Clin Med. 2018;7(4).

[3] Garcia-Prat L, Martinez-Vicente M, Perdiguero E, et al. Autophagy maintains stemness by preventing senescence. Nature.2016;529(7584):37-42.

[4] Frontera WR, Hughes VA, Fielding RA, et al. Aging of skeletal muscle: A 12-yr longitudinal study. J Appl Physiol (1985).2000;88(4):1321-1326.

[5] Larsson L. Histochemical characteristics of human skeletal muscle during aging. Acta Physiol Scand. 1983;117(3):469-471.

[6] Rizzoli R, Reginster JY, Arnal JF, et al. Quality of life in sarcopenia and frailty. Calcif Tissue Int. 2013;93(2):101-120.

[7] Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing.2019;48(1):16-31.

[8] Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: Consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95-101.

[9] Chen LK, Lee WJ, Peng LN, et al. Recent advances in sarcopenia research in asia: 2016 update from the asian working group for sarcopenia. J Am Med Dir Assoc.2016;17(8):761-767.

[10] Cruz-Jentoft AJ, Landi F, Schneider SM, 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( 6):748-759.

[11] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing.2010;39(4):412- 423.

[12] Hepple RT, Rice C L. Innervation and neuromuscular control in ageing skeletal muscle. J Physiol. 2016;594(8):1965-1978.

[13] Tintignac LA, Brenner HR, Ruegg M A. Mechanisms regulating neuromuscular junction development and function and causes of muscle wasting. Physiol Rev.2015;95(3):809-852.

[14] Rudolf R, Deschenes MR, Sandri M. Neuromuscular junction degeneration in muscle wasting. Curr Opin Clin Nutr Metab Care. 2016;19(3):177-181.

[15] Sandri M, Sandri C, Gilbert A, et al. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. Cell. 2004;117(3):399-412.

[16] Mammucari C, Milan G, Romanello V, et al. FoxO3 controls autophagy in skeletal muscle in vivo. Cell Metab. 2007;6(6):458-471.

[17] Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: Prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc.2011;12 (4):249-256.

[18] Giovannini S, Marzetti E, Borst SE, et al. Modulation of GH/IGF-1 axis: Potential strategies to counteract sarcopenia in older adults. Mech Ageing Dev.2008;129(10):593-601.

[19] Brioche T, Kireev RA, Cuesta S, et al. Growth hormone replacement therapy prevents sarcopenia by a dual mechanism: Improvement of protein balance and of antioxidant defenses. J Gerontol A Biol Sci Med Sci. 2014;69(10): 1186-1198.

[20] Salomon F, Cuneo RC, Hesp R, et al. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med.1989;321(26):1797- 1803.

[21] Rudman D, Kutner MH, Rogers CM, et al. Impaired growth hormone secretion in the adult population: Relation to age and adiposity. J Clin Invest. 1981;67(5):1361-1369.

[22] Baumgartner RN, Waters DL, Gallagher D, et al. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev.1999;107(2):123-136.

[23] Morley JE, Kaiser FE, Perry HR, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism.1997;46(4):410-413.

[24] Messier V, Rabasa-Lhoret R, Barbat-Artigas S, et al. Menopause and sarcopenia: A potential role for sex hormones. Maturitas. 2011;68(4):331-336.

[25] Sorensen MB, Rosenfalck AM, Hojgaard L, et al. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001;9(10):622-626.

[26] Smith GI, Atherton P, Villareal DT, et al. Differences in muscle protein synthesis and anabolic signaling in the postabsorptive state and in response to food in 65-80 year old men and women. PLoS One.2008;3(3 ): e1875.

[27] Hansen M. Female hormones: Do they influence muscle and tendon protein metabolism? Proc Nutr Soc.2018;77(1):32-41.

[28] Miller BF, Hansen M, Olesen JL, et al. No effect of menstrual cycle on myofibrillar and connective tissue protein synthesis in contracting skeletal muscle. Am J Physiol Endocrinol Metab. 2006;290(1):E163-E168.

[29] Kenny AM, Prestwood KM, Gruman CA, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci.2001;56(5):M266-M272 .

[30] Cleasby ME, Jamieson PM, Atherton P J. Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. J Endocrinol.2016;229(2):R67-R81.

[31] Rommel C, Bodine SC, Clarke BA, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nat Cell Biol .2001;3(11):1009-1013.

[32] Meng SJ, Yu L J. Oxidative stress, molecular inflammation and sarcopenia. Int J Mol Sci. 2010;11(4):1509-1526.

[33] Katta A, Kundla S, Kakarla SK, et al. Impaired overload-induced hypertrophy is associated with diminished mTOR signaling in insulin-resistant skeletal muscle of the obese Zucker rat. Am J Physiol Regul Integr Comp Physiol. 2010;299( 6): R1666-R1675.

[34] Wang X, Hu Z, Hu J, et al. Insulin resistance accelerates muscle protein degradation: Activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology.2006;147(9):4160-4168.

[35] Srikanthan P, Karlamangla A S. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab.2011;96(9):2898-2903.

[36] Moon MK, Lee YJ, Choi SH, et al. Subclinical hypothyroidism has little influences on muscle mass or strength in elderly people. J Korean Med Sci. 2010;25(8):1176-1181.

[37] Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care. 2012;15(1):12-22.

[38] Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: The Health ABC Study. J Gerontol A Biol Sci Med Sci .2002;57(5):M326-M332.

[39] Lieffers JR, Bathe OF, Fassbender K, et al. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107(6):931-936.

[40] O'Toole PW, Jeffery I B. Gut microbiota and aging. Science. 2015;350(6265):1214-1215.

[41] Siddharth J, Chakrabarti A, Pannerec A, et al. Aging and sarcopenia associate with specific interactions between gut microbes, serum biomarkers and host physiology in rats. Aging (Albany NY).2017;9(7):1698-1720 .

[42] Bindels LB, Beck R, Schakman O, et al. Restoring specific lactobacilli levels decreases inflammation and muscle atrophy markers in an acute leukemia mouse model. PLoS One.2012;7(6):e37971.

[43] Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: A randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc. 2015;16(9):740-747.

[44] Beaudart C, Buckinx F, Rabenda V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: A systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab.2014 ;99(11):4336-4345.

[45] Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): The Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003;88(12 ):5766-5772.

[46] Wilkinson SB, Tarnopolsky MA, Macdonald MJ, et al. Consumption of fluid skim milk promotes greater muscle protein accretion after resistance exercise than does consumption of an isonitrogenous and isoenergetic soy-protein beverage. Am J Clin Nutr. 2007;85( 4):1031-1040.

[47] Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: A randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc.2012;13(8 ):720-726.

[48] ​​Miao Qin, Wang Leilei, He Fang, et al. The effect of enteral nutrition preparations on muscle strength and muscle content in patients with muscle attenuation syndrome[J]. Clinical and Education of General Practice, 2016(05):499-502 .

[49] Stipanuk M H. Leucine and protein synthesis: MTOR and beyond. Nutr Rev. 2007;65(3):122-129.

[50] Lozano-Montoya I, Correa-Perez A, Abraha I, et al. Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients: A systematic overview-the SENATOR Project ONTOP Series. Clin Interv Aging.2017;12:721 -740.

[51] D'Souza RF, Marworth JF, Figueiredo VC, et al. Dose-dependent increases in p70S6K phosphorylation and intramuscular branched-chain amino acids in older men following resistance exercise and protein intake. Physiol Rep. 2014;2(8) .

[52] Symons TB, Sheffield-Moore M, Wolfe RR, et al. A moderate serving of high-quality protein maximally stimulates skeletal muscle protein synthesis in young and elderly subjects. J Am Diet Assoc.2009;109(9):1582 -1586.

[53] Burd NA, Yang Y, Moore DR, et al. Greater stimulation of myofibrillar protein synthesis with ingestion of whey protein isolate v. Micellar casein at rest and after resistance exercise in elderly men. Br J Nutr.2012;108(6 ):958-962.

[54] Pennings B, Koopman R, Beelen M, et al. Exercising before protein intake allows for greater use of dietary protein-derived amino acids for de novo muscle protein synthesis in both young and elderly men. Am J Clin Nutr. 2011; 93(2):322-331.

[55] Tessier AJ, Chevalier S. An update on protein, leucine, omega-3 fatty acids, and vitamin d in the prevention and treatment of sarcopenia and functional decline. Nutrients.2018;10(8).

[56] Clark DJ, Patten C, Reid KF, et al. Muscle performance and physical function are associated with voluntary rate of neuromuscular activation in older adults. J Gerontol A Biol Sci Med Sci. 2011;66(1):115-121 .

[57] Melov S, Tarnopolsky MA, Beckman K, et al. Resistance exercise reverses aging in human skeletal muscle. PLoS One.2007;2(5):e465.

[58] Harridge SD, Kryger A, Stensgaard A. Knee extensor strength, activation, and size in very elderly people following strength training. Muscle Nerve.1999;22(7):831-839.

[59] Liao CD, Tsauo JY, Lin LF, et al. Effects of elastic resistance exercise on body composition and physical capacity in older women with sarcopenic obesity: A CONSORT-compliant prospective randomized controlled trial. Medicine (Baltimore).2017;96 (23):e7115.

[60] Galvao DA, Taaffe DR, Spry N, et al. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: A randomized controlled trial. J Clin Oncol.2010;28( 2):340-347.

[61] Johannsmeyer S, Candow DG, Brahms CM, et al. Effect of creatine supplementation and drop-set resistance training in untrained aging adults. Exp Gerontol.2016;83:112-119.

[62] Phillips S M. Nutritional supplements in support of resistance exercise to counter age-related sarcopenia. Adv Nutr. 2015;6(4):452-460.

[63] Salazar-Degracia A, Busquets S, Argiles JM, et al. Effects of the beta2 agonist formoterol on atrophy signaling, autophagy, and muscle phenotype in respiratory and limb muscles of rats with cancer-induced cachexia. Biochimie.2018;149 :79-91.

[64] Gouspillou G, Picard M, Godin R, et al. Role of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) in denervation-induced atrophy in aged muscle: Facts and hypotheses. Longev Healthspan. 2013; 2(1): 13.

[65] Yokokawa T, Kido K, Suga T, et al. Exercise training increases CISD family protein expression in murine skeletal muscle and white adipose tissue. Biochem Biophys Res Commun. 2018;506(3):571-577.

[66] Long DE, Peck BD, Martz JL, et al. Metformin to Augment Strength Training Effective Response in Seniors (MASTERS): Study protocol for a randomized controlled trial. Trials. 2017;18(1):192.

[67] Band MM, Sumukadas D, Struthers AD, et al. Leucine and ACE inhibitors as therapies for sarcopenia (LACE trial): Study protocol for a randomised controlled trial. Trials.2018;19(1):6.

[68] Lin CH, Yang H, Xue QL, et al. Losartan improves measures of activity, inflammation, and oxidative stress in older mice. Exp Gerontol.2014;58:174-178.