Review

A review of Parkinson's disease combined with sarcopenia in the elderly

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Abstract

Sarcopenia is an aging-associated muscle disease characterised by loss of skeletal muscle mass and strength, with or without loss of physical performance, which can increase the risk of falls, fractures, disability and death. Parkinson's disease (PD) is the second most common neurodegenerative disease and one of the diseases with the greatest increase in prevalence, disability and mortality in recent years. The occurrence of sarcopenia is more prevalent in patients with PD. In order to improve the survival status and prognosis of patients with PD combined with sarcopenia, this article reviews the progress of research related to the epidemiology, diagnostic criteria, pathogenesis, adverse outcomes, and treatment of PD combined with sarcopenia at home and abroad in recent years.

Keywords: sarcopenia; Parkinson's disease; diagnosis; pathogenesis

Introduction

Since the first definition of sarcopenia in 1988, several definitions of sarcopenia have been developed by different working groups or societies, with the most used definition being developed by the European Working Group on Sarcopenia in Older People (EWGSOP): sarcopenia is an ageing-associated muscular disease characterised by loss of skeletal muscle mass and strength with or without loss of physical performance, which can increase the fall, fracture, disability and death risk[1].The increasing prevalence of sarcopenia has become a serious global public health problem, posing a serious threat to the quality of life and survival prognosis of patients. It is characterised by a loss of muscle mass and strength associated with aging and chronic diseases such as PD [1].PD is the second most common neurodegenerative disease and one of the diseases with the greatest increase in prevalence, disability and mortality in recent years [2]. It is expected that by 2030, there will be approximately 5 million PD patients in China, accounting for about half of the PD patients worldwide [3]. Its clinical features are characterised by motor symptoms such as bradykinesia, resting tremor, rigidity and postural instability.Motor symptoms in patients with PD can lead to a decrease in muscle strength, performance and muscle mass [4]. PD is involved in the development of sarcopenia, and the clinical presentation and severity of PD is a determining factor that directly affects sarcopenia [5].

Neurodegenerative diseases and muscle loss associated with aging increase the risk of PD sarcopenia in older adults, seriously affecting their physical and psychological health. Effective screening and rational diagnosis and treatment of sarcopenia are of great significance in improving the quality of life of the elderly and alleviating the medical and economic pressure on the society. In this article, we review the progress of research on the epidemiology, diagnostic criteria, mechanisms, adverse effects and treatment of PD sarcopenia at home and abroad, with the aim of strengthening the national awareness, improving the identification, prevention and treatment capabilities, and improving the survival and prognosis of PD patients with sarcopenia.

Epidemiology of Parkinson's disease combined with sarcopenia

Currently, the overall prevalence of sarcopenia in community-dwelling populations is 10 per cent globally[6]. However, the prevalence of sarcopenia tends to vary according to different diagnostic criteria: the prevalence of sarcopenia in the general

population according to the EWGSOP, EWGSOP2 and Asian Working Group on Sarcopenia (AWGS) classifications is 22%, 10% and 15%, respectively [7]. The prevalence of sarcopenia is higher in patients with PD than in age- and sex-matched healthy elderly controls [8-10]. The prevalence of sarcopenia in PD ranges from 10.9% to 31.4% [11]. In PD patients, sarcopenia is significantly more prevalent in men than in women, which may be due to the fact that female PD patients exposed to the same dose of levodopa as male controls have more side effects due to low body weight, such as dyskinesia, which acts as an exercise, increases energy expenditure, and affects body composition[9]. However, the prevalence of sarcopenia in PD varies in different studies. According to EWGSOP2010, the prevalence of sarcopenia in PD ranges from 6-31.4% [8, 9, 12, 13]；according to AWGS2019, the prevalence of sarcopenia is 40%[10]. Differences between these studies may be related to diagnostic criteria, muscle mass measurement techniques, different thresholds for the muscle mass index used to define sarcopenia, and the inclusion of patients with PD with their own characteristics [14].

Diagnosis of sarcopenia

1. Main diagnostic methods

1.1 Screening

Calf circumference and the SARC-F questionnaire: Calf circumference is measured using a non-elastic band to measure the maximum circumference of the calves bilaterally, and the "finger-ring test" can be used as a valid alternative to measuring calf circumference.The SARC-F questionnaire involves five functional statuses of older adults, and the scale has low sensitivity and high specificity, which allows for the accurate identification of impaired physical function and is associated with poor clinical outcomes[15]. The SARC-F has the advantage of being a simple, rapid and effective screening tool that is independent of instrumentation and thresholds, and independent of age and gender differences.The addition of calf circumference to the SARC-CalF questionnaire improves the sensitivity of the SARC-F.

1.2 Muscle strength

Upper extremity grip strength has been widely recognised as an indicator of muscle strength. The most commonly used grip strength measurement is the spring-loaded grip strength device, followed by the hydraulic grip strength device. The use of two types of grip strength devices: (1) hydraulic grip strength device: take a sitting position, 90 °elbow flexion to measure grip strength; (2) spring-loaded grip strength

device: standing position, elbow extension to measure grip strength; if the elderly can not stand independently, then choose to sit to measure. Use the dominant hand or both hands respectively, maximum force isometric contraction, at least 2 tests, select the maximum reading. In addition, it is recommended to use an electronic grip strength device with a digital display to ensure the accuracy of the data.

1.3 Skeletal muscle mass

The most commonly used instruments for measuring skeletal muscle mass(SMM) are Dual Energy X-ray Absorptiometry (DXA) and Bioelectrical Impedance Analysis (BIA).BIA calculates percent body fat from electrical impedance, and its measurements are highly correlated with body water content. DXA is highly accurate, has low radiation exposure, is easy to perform, and is capable of evaluating regional distributions of fat and muscle. The multi-frequency BIA instrument is the closest to the DXA measurements of extremity SMM.So AWGS2019 recommends using either the DXA or multi-frequency BIA in combination with height correction to measur SMM. [16].

1.4 Physical function

The Simple Physical Performance Battery (SPPB), step speed, The five-repetition sit-to-stand test（5STS）, the Time-Up-Go test (TUG), and the 400m walk test were used to assess somatic function. The SPPB is a comprehensive somatic function test tool with three components: the three-posture test, including standing with feet together, standing with feet in a half tandem anteroposteriorly and anteriorly and posteriorly and standing with feet in a tandem anteriorly and posteriorly, with each posture being tested for 10s; the gait test; and the 5STS.Step speed is the simplest, quickest and safest method of assessing somatic function. TUG measures the time it takes to walk a certain distance at a normal walking speed from the start of movement, without acceleration or deceleration, and is measured at least twice, with the average speed recorded.TUG can reflect the individual's balance and walking ability. The TUG measures the time it takes for a subject to rise from a seat of about 46cm in height, complete a 3m round trip walk at the fastest and steadiest speed, and finally sit back in the chair, and the measurement is repeated at least twice, with the shortest time recorded. 400m walk can test the walking ability and endurance of the elderly. Subjects are required to complete the walk as fast as they can, with up to 2 breaks. Due to its long duration and high physical demands, it is not suitable for the elderly or frail, and is currently only used in scientific research.

2. Cutoff value for diagnosis

Currently, EWGSOP, the International Working Group on Sarcopenia (IWGS), AWGS, and Foundation for the National Institutes of Health (FNIH) have developed and recommended parameters and diagnostic cut-points for the assessment of sarcopenia that are appropriate for their own regional populations, which mainly include 3 aspects of muscle mass, muscle strength, and somatic capacity, as shown in Table 1. Comparing AWGS2019 and AWGS2014, the diagnosis of sarcopenia has been updated in terms of grip strength and step speed thresholds. Assessment of somatic function is no longer limited to step speed, and the 5STS and SPPB can be used in place of step speed. In addition, the AWGS2019 Working Group updated the diagnostic criteria and proposed a screening programme for the community and hospitals, recommending first screening for calf circumference (< 34 cm in men and < 33 cm in women) or use of the SARC-F (≥ 4 points) or SARC-CalF (≥ 11 points) questionnaires to facilitate early identification of people at risk of sarcopenia. EWGSOP2018 and AWGS2019 differ slightly in their diagnostic strategies. The definition of sarcopenia by EWGSOP2018 [1] emphasises muscle strength as the primary indicator, confirms the diagnosis of sarcopenia by detecting low muscle number and mass, and identifies poorer physical performance as a marker of severe sarcopenia.AWGS2019 [16] suggests that declines in both muscle strength and somatic functioning are the result of declines in muscle mass, and that they have a detrimental impact on prognosis. Therefore sarcopenia can be diagnosed whenever there is a decrease in muscle strength or function combined with a decrease in muscle mass. Severe sarcopenia is diagnosed if there is a decrease in both muscle strength and function.

3. Diagnostic algorithm

According to AWGS 2019 [16], the diagnostic process of sarcopenia mainly includes two parts: community primary medical institutions and clinical medical institutions. Cases were detected by measuring calf circumference or SARC-CalF in community primary care Settings, and then evaluated by grip strength and five times sit up time. Lifestyle intervention and related health education are recommended for residents with possible sarcopenia, and referral to hospitals for diagnosis is also encouraged. In hospital and institutional diagnostic algorithms, initial evaluation is considered when a patient presents with typical symptoms of sarcopenia, such as muscle wasting, falls, and abnormal gait characterized by slow walking. Muscle

strength, physical function, and appendicular skeletal muscle mass were assessed. On the basis of the diagnosis of sarcopenia, if there is a simultaneous decline in muscle strength and function, it is considered as severe sarcopenia.

Pathogenesis of Parkinson's disease with sarcopenia

1. Disruption of the neuromuscular junction

Disruption of the neuromuscular junction (NMJ) is common in several neurodegenerative diseases, including PD [17],and can induce downstream sarcopenia phenotypes, reflecting the key role of the NMJ in maintaining muscle health [18]. NMJ dysfunction often precedes muscle damage and may exacerbate the postsynaptic changes in PD-related sarcopenia[18]. The NMJ is a plastic structure that can achieve self-repair with exercise and other interventions [19]. Studies have found that exercise can maintain the plasticity of the NMJ in rodents and restore the structure and function of the NMJ in humans[20]. Neurotrophin and CAF22b have been implicated in NMJ disruption and muscle degeneration. Circulating levels of these biomarkers are significantly altered in the early stages of PD, while biomarker levels partially return to normal levels in patients after rehabilitation treatment [21].

Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are released by muscle fibers, motor neurons, and adjacent Schwann cells and are mainly used to maintain NMJ function and mediate axon sprouting and acetylcholine receptor aggregation after denervation[22]. Plasma BDNF and GDNF levels are low in PD patients[22] , which weakens the neuroprotective ability of BDNF and GDNF and may lead to NMJ dysfunction and decreased muscle function. The loss of muscle mass and strength in the elderly is also partially attributed to the diminished protective effects of BDNF and GDNF [23]. The expression of BDNF and GDNF in the tissues of PD patients has plasticity. Exercise intervention can increase plasma BDNF and GDNF levels in the elderly , thereby improving the neuroprotective ability of BDNF and GDNF[24, 25].

Aggrecan is a neuronal proteoglycan composed of two aggrecan fragments. C-terminal aggregation protein fragment 22 (CAF22) is one of the smaller fragments, which is a circulating biomarker of NMJ destruction and sarcopenia in the elderly [26]，and is released into the blood circulation as a stable non-bioactive molecule[22]. The study by Karim et al.[21]found that patients before treatment had a significant reduction in grip strength and a significant increase in plasma CAF22 levels. Rehabilitation training can reduce plasma CAF22 levels while restoring grip strength,

and promote NMJ recovery and muscle health.

2. Chronic inflammation

Chronic inflammation is considered as a potential pathological condition[27]. Elevated levels of circulating inflammatory mediators, including interleukin-6(IL-6) and tumor necrosis factor-α(TNF-α), were detected in both patients with early PD and those with sarcopenia. High levels of IL-6 can lead to sarcopenia[28]. A randomized controlled trial of 99 older adults with limited mobility identified an age-related increase in circulating IL-6 levels as a key factor in the decline in skeletal muscle strength, mass, and function[29]. Pelosi et al. observed the effects of high levels of IL-6 on NSE/IL-6 mice and found that IL-6 may cause muscle atrophy by promoting an increase in glycolytic metabolism[30].

A meta-analysis showed that older adults with sarcopenia had higher levels of TNF-α, indicating that high levels of TNF-α were associated with an increased risk of sarcopenia[31]. Increased plasma concentrations of TNF-α were associated with lower muscle mass, strength, and activation of apoptosis in muscle cells. TNF-α activates local vascular endothelial cells, leading to the release of nitric oxide, which in turn increases vascular permeability and allows passage of proinflammatory cells, ultimately causing inflammation [32]. TNF-α can also promote muscle atrophy by activating the nuclear factor-kB (NF-Kb) pathway, up-regulating muscle ring finger protein-1 (MuRF-1), and activating the ubiquitin-proteasome pathway [33]. Pyroptosis mediated by TNF-α/caspase-8/caspase-3/GSDME signaling pathway is a new mechanism for the occurrence and development of sarcopenia. Caspase-3/GSDME signaling pathway mediated pyroptosis may be a promising therapeutic target for sarcopenia [34].

3. Impaired autophagy function of muscle fibers

Impaired autophagy function of muscle fibers is the common pathophysiological mechanism of muscle fiber loss in sarcopenia and PD [13]. Autophagy regulates inflammatory cytokines by inhibiting oxidative stress to maintain the normal function of muscle fiber organelles and cells [35, 36]. Autophagy dysfunction disrupts cellular homeostasis, impairs mitochondrial function, aggravates oxidative stress, accelerates cell senescence, and damages muscle satellite cells [37]. Satellite cells are located between the basement and sarcolemmal membranes of muscle fibers in a mitotically quiescent state, and these cells are activated and proliferate in response to stimuli such

as physical exercise, injury, or mechanical stress. Insulin-like growth factor-1(IGF-1) is closely related to the differentiation and proliferation of muscle satellite cells and the fusion of muscle cells [38, 39]. Inhibition of autophagy may reduce growth hormone receptor (GHR) and IGF-1 to inhibit satellite cell regeneration[40]. Oxidative stress refers to the imbalance between oxidative and antioxidant regulation. Several evidences suggest that the Kelch-like ECH-associated protein 1 (Keap1) -nuclear factor-erythroid 2-related factor 2 (Nrf2) system is closely related to oxidative stress, and its signaling is also regulated by phosphatidylinositol 3 kinase (PI3K)/protein kinase B (PKB, also known as Akt), PKC and mitogen-activated protein kinase[41]. Autophagy plays a protective role in oxidative stress by promoting the competitive binding of Nrf2 by p62 instead of Keap1 and inhibiting the degradation of Nrf2[42]. Impaired autophagy leads to reduced inhibition of Nrf2 degradation, increased ROS production and oxidative stress markers. The NF-κB signaling pathway is known to promote inflammatory activation. Related studies have found that inhibition of autophagy may activate the NF-κB signaling pathway, generate the NLRP3 inflammatome, promote the expression of inflammatory factor IL-1β, inhibit the anabolic metabolism of myocytes, and induce sarcopenia[43-45]. FOXOs members are the most widely known transcription factors downstream of the AKT/IGF-1/ insulin pathway, and their activity can be regulated by a variety of enzymes or by transcription factors. In humans, four FOXOs have been identified, among which FOXO1 and FOXO3 are involved in muscle atrophy, regulation of autophagy gene transcription and aberrant autophagy[46, 47]. FOXOs are induced by adenosine 5 '-monophosphP-activated protein kinase (AMPK) to translocate into the nucleus and persist in muscle atrophy[48].

4. Motor neuron reduction

The effects of PD on skeletal muscle include decreased muscle strength, endurance, and muscle atrophy[17]. These effects can be explained in part by the death of motor neurons, and this continued denervation accelerates the onset of sarcopenia. A reduction in the number of motor neurons is a common feature of both sarcopenia and PD[49]. The transcription factor NF-κB is a key intracellular signaling molecule in denervation leading to muscle atrophy[50]. The transcription factor NF-κB is a key intracellular signaling molecule in denervation leading to muscle atrophy[32]. These effects can be explained in part by the death of motor neurons, and this continued denervation accelerates the onset of sarcopenia. A reduction in the number of motor

neurons is a common feature of both sarcopenia and PD[12]. Neuronal apoptosis may be the mechanism of motor neuron reduction in PD patients with sarcopenia. The mitochondrial permeability transition pore (mPTP) is a weakly selective large conductive channel that is closed under non-stress conditions and can be triggered to open by reactive oxygen species (ROS) and Ca2+ overload produced by mitochondria. Excessive opening of mPTP results in an imbalance of mitochondrial membrane potential and subsequent release of mitochondrial contents, such as ROS and cytochrome c, into the cytoplasm, thereby initiating an apoptotic signaling cascade in motor neurons and myofibers. Activation of apoptotic signals is accompanied by DNA fragmentation and nuclear apoptosis, which eventually leads to muscle atrophy and denervation [51].

5. Brain structure and network changes

Changes in brain structure and networks play a key role in the pathophysiology of PD patients with sarcopenia. Decreased gray matter volume in specific regions of PD patients, such as the uncinate gyrus and superior temporal gyrus, is significantly associated with core muscle loss [52]. The reduced size of the default mode network results in insufficient activity of the task-related network, resulting in poor motion function [52]. Compared with PD patients without sarcopenia, sarcopenia showed the strongest correlation with muscle mass loss by diffusion tensor imaging (DTI), which represents white matter changes in the executive function network of PD patients with sarcopenia [53]. Furthermore, reduced ASMI was associated with reduced fractional anisotropy of frontostriato-thalamic circuits in sarcopenic PD patients [53].

6. Sex hormone deficiency

PD patients with sarcopenia may be affected by the changes of sex hormones. Androgens play an important role in the maintenance of muscle mass. Low plasma testosterone levels can cause or accelerate muscle and age-related diseases. In addition to the natural decline in testosterone levels with age, abnormalities in plasma testosterone levels can be observed in endocrine diseases such as late-onset hypogonadism, decreased androgen production, and accelerated testosterone metabolism [54]. However, no studies have investigated the relationship between testosterone and sarcopenia in PD patients, and future studies are needed to clarify this.

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no studies have investigated the relationship between testosterone and sarcopenia in PD patients, and future studies are needed to clarify this[56]. However, no studies have investigated the relationship between testosterone and sarcopenia in PD patients, and future studies are needed to clarify this [56] . These inflammatory factors can degrade muscle proteins and reduce the ability of adult muscles to respond to injury. Estradiol inhibits the occurrence of sarcopenia by regulating local and systemic inflammatory responses [57, 58].

7. Mitochondrial dysfunction

Mitochondrial dysfunction has been demonstrated in non-neuronal tissues of PD patients, and it has been shown that mitochondrial abnormalities are more common in PD with sarcopenia than in healthy older muscles [11] . ROS includes superoxide anions, hydroxyl radicals and hydrogen peroxide, and the most important ROS production in muscle cells is located in the mitochondria. ROS causes progressive damage to key cellular macromolecules, including lipids, proteins, and DNA, thereby altering their structure and function. Denervation or NMJ degeneration significantly increases the production of peroxides in muscle mitochondria while eliminating the interaction between motor neurons and muscle, resulting in significant defects in muscle regeneration [59]. Yang et al. [60] found that oxidative stress induced by α-synuclein (α-Syn) aggregation might be a new idea for muscle atrophy in PD patients. Aggregation of α-Syn results in an increased number of swollen and broken cristae structure mitochondria in intramuscular axons and NMJS. At the same time, the expression of genes related to ROS metabolism decreased, resulting in increased oxidative stress of intramuscular mitochondria. In addition, mitochondrial dysfunction may also be the result of failure of mitochondrial quality control (MQC) processes, including protease homeostasis, biogenesis, dynamics, and mitophagy [61].

Adverse outcomes

1.Fall

Falls are a serious problem in PD patients with sarcopenia. Patients with PD and sarcopenia have an increasing risk of falling compared to healthy individuals and patients with other neurological conditions such as polyneuropathy, spinal disease, and multiple sclerosis [49]. Older adults taking anti-PD medications have a higher risk of exposure to fall-inducing medications. The more advanced the disease, the more drugs they need, and the less independent these patients are [49]. Clinical

manifestations associated with sarcopenia, such as reduced mobility, poor balance, and reduced leg muscle strength, are associated with increased risk of falls [62]. Studies had shown that disease duration, freezing of gait, postural instability, non-motor symptoms, and high levodopa equivalent daily dose (LEDD) were also associated with the occurrence of falls [9, 49, 63]. From the perspective of prognosis, compared with non-fallers, frequent fallers have a longer course of disease and worse prognosis [64]. From the perspective of prognosis, compared with non-fallers, frequent fallers have a longer course of disease and worse prognosis.

2. Disability

Disability is defined as impairment in the ability to perform basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Individuals with PD and sarcopenia have greater difficulty with ADL and IADL [65]. Musculoskeletal conditions and motor and nonmotor symptoms of PD affect life skills, and these challenges increase with aging and neurodegenerative disease progression. Muscle strength is strongly associated with severity of PD and disability, and sarcopenia, defined using the SARC-F questionnaire, is a good predictor of disability in PD [9].

3. Fracture

The occurrence of fractures is influenced by two main factors: on the one hand, the neuro-musculoskeletal changes accompanying PD and impaired postural stability due to reduced leg muscle strength can lead to falls, which cause traumatic injuries-fractures; on the other hand, PD and the use of levodopa increases the risk of osteoporosis [66].

4. Dysphagia

Age and disease characteristics are high risk factors for dysphagia in patients with PD, and muscle mass is lower in patients with PD compared to healthy controls and more pronounced in PD patients with dysphagia [4].Chronic denervation and reinnervation are secondary to systemic neurodegeneration, resulting in pharyngeal atrophy of the swallowing muscle in PD patients with dysphagia [67]. Dysphagia can lead to inadequate drug intake, malnutrition, dehydration, and aspiration pneumonia, which is the leading causes of death in PD patients [68].

5. Loss of weight

Weight loss and reduced body mass index are common in PD patients due to altered energy expenditure, impaired homeostatic regulation, and gastrointestinal dysfunction [10]. Weight loss may precede the diagnosis of PD and often worsens as the disease progresses, leading to an increased risk of malnutrition, fractures, pressure ulcers, and death [10].

Treatment of Parkinson's disease with sarcopenia

1. Non-drug treatment

1.1 Exercise therapy

Exercise is considered to be one of the most commonly used treatments to improve sarcopenia in PD patients[1, 69]. Liver growth factor (HGF) is attached to the extracellular matrix and is released after physical activity to repair tissue damage caused by exercise and can activate muscle satellite cells. Exercise promotes the production of nitric oxide (NO) in the body, and NO is a key signal for HGF activation. Lack of exercise or disuse leads to reduced NO production, which in turn affects HGF release from the extracellular matrix, keeping muscle satellite cells in the G0 phase of the cell cycle [32]. Resistance exercise has been shown to be beneficial for sarcopenia and is widely accepted by patients as a treatment [70, 71]. In one study, significant improvements in SMM, muscle function, and NMJ integrity index were found in PD patients after 16 weeks of resistance training. Whole-transcriptome skeletal muscle RNA sequencing of skeletal muscle of PD patients before and after resistance training found that genes related to nervous system and muscle development were significantly up-regulated, and genes negatively regulated by muscle adaptation were down-regulated [72]. Exercise can stimulate the transfer of muscle mitochondria and mitochondrial DNA (mtDNA) through extracellular vesicles to repair damaged neuronal mitochondria [73]. Exercise-induced autophagy is beneficial for the treatment of sarcopenia by regulating Akt/mTOR and Akt/FoxO3a signaling pathways and AMPK-mediated MQC[74]. In addition, the ubiquitin-proteasome system(UPS) is one of the major pathways involved in muscle protein degradation. This system plays a key role in controlling muscle fiber size. In this degradation mechanism, specific ligases bind ubiquitin to substrate proteins in order to initiate their proteolysis. Exercise can activate AMPK/PGC-1α signaling pathway and inhibit UPS damage, excessive apoptosis, autophagy defects and mitochondrial dysfunction, thereby preventing and delaying sarcopenia [75]. Skeletal muscle contraction stimulates the release of BDNF and activates cyclic-AMP

response element binding protein (CREB) to stimulate DNA repair [32].

1.2 Nutritional therapy

Muscle-targeting oral nutritional supplements may be an effective treatment for PD patients with sarcopenia. Muscle-targeted oral nutritional supplements are whey protein-based formulations rich in leucine and vitamin D [76]. Whey protein has been shown to be a valuable source of protein by rapidly increasing plasma essential amino acid levels, thereby stimulating muscle protein synthesis [77]. Whey proteins are capable of producing a variety of dipeptide and tripeptide hydrolysates, known as antisarcopenia peptides, which are more readily absorbed than free amino acids [78]. They play a key role by activating the PI3K/Akt/mTOR and MAPK pathways and inhibiting the UPS and AMPK pathway, thereby promoting the synthesis and inhibiting the degradation of muscle proteins [79]. Leucine has a positive effect on protein turnover in regulating skeletal muscle anabolism, protein synthesis, and autophagy [80]. Leucine can stimulate muscle protein synthesis and inhibit protein degradation through mTOR signaling pathway, and further effectively improve sarcopenia [79]. Vitamin D deficiency can promote the expression of related proteins and regulate the synthesis and degradation of skeletal muscle proteins. The study found that vitamin D deficiency increased protein expression of MuRF1, muscle atrophy F-box (MAFbx), and FOXO3a [81]. MAFbx catalyzes protein degradation and promotes and controls protein synthesis by regulating eukaryotic initiation factor 3 (eIF3f)[82]. MuRF1 selectively binds to and promotes fibrin ubiquitination, thereby increasing protein degradation by the 26S proteasome [83]. A pragmatic, bi-center, randomized assessor-blinded controlled trial found that consumption of a whey protein formula rich in leucine and vitamin D improved lower limb function and preserved muscle mass in patients with PD [84]. In a single-center, double-blind, randomized, controlled trial, consumption of a whey protein nutritional formula rich in leucine and vitamin d improved physical function and muscle mass. [85].Therefore, it further suggests the feasibility of muscle-targeted oral nutritional supplements in the prevention and treatment of PD patients with sarcopenia.

1.3 Exercise combined with nutrition therapy

Resistance exercise combined with nutritional supplements can significantly improve patients' physical function, muscle mass and strength [16] . Taking a formula rich in leucine and vitamin D, combined with rehabilitation exercise for people with PD,

improves walking distance and speed and increases muscle mass more than rehabilitation alone [84]. The study found that participants who took whey protein after resistance exercise had increased muscle mass, grip strength and gait speed compared to those in any single intervention group [86]. Therefore, exercise combined with nutrition therapy is superior to a single treatment in PD patients with sarcopenia.

Drug therapy

There are currently no specific drugs approved for the treatment of PD patients with sarcopenia [87]. However, some drugs used in clinical or scientific research have been shown to benefit muscles. Therefore, we summarize the potential benefits of these drugs on muscle and provide new directions for the treatment of sarcopenia.

Inflammation plays a crucial role in the pathogenesis of PD with sarcopenia. Therefore, targeted therapy against inflammatory factors associated with sarcopenia may be an effective strategy to improve sarcopenia [87]. TNF-α and IL-6 promote chronic inflammation and affect skeletal muscle capacity, which are regarded as potential therapeutic targets for sarcopenia. TNF-α inhibitor etanercept can inhibit fiber type transition, inhibit muscle loss, improve muscle function, and prolong the life span of aging mice [88, 89]. Patients with rheumatoid arthritis had increased skeletal muscle mass in the extremities with tocilizumab, an anti-IL-6 receptor monoclonal antibody, as compared with untreated patients [90].

Irisin is an exercise-induced polypeptide hormone secreted by muscle and produced by FNDC5 proteolysis, which is also a biomarker of sarcopenia [91]. Several lines of evidence suggest that PI3K/Akt/Nrf2 is a therapeutic target for oxidation/reduction (REDOX) reactions imbalance and age-related diseases [41]. Irisin protects skeletal muscle by reducing REDOX imbalance and fibrosis by regulating the PI3K/Akt signaling pathway [91]. Irisin plays a neuroprotective role in PD by reducing the loss of dopaminergic neurons and promoting lysosomal degradation of pathological α-syn in PD mouse models [92]. In addition, irisin triggers the expression of brain-derived neurotrophic factor, which crosses the blood-brain barrier, enhances mitochondrial biogenesis in neurons, and reduces dopaminergic loss in animal models of PD [93].

Angiogenic factor-1 (AGGF1) is a biologically active substance that stimulates the formation of new blood vessels and usually plays a role in growth, development, and repair. [94]. A recent study found that intramuscular and intraperitoneal injection of recombinant AGGF1 protein can alleviate the atrophy phenotype of denervated mice.

This may be due to AGGF1 may promote skeletal muscle autophagy and inhibit MuRF1 expression through AGGF1-TWEAK (tumor necrosis factor-like weak inducer of apoptosis)/Fn14-NF-κB signaling pathway. Finally, skeletal muscle atrophy was alleviated. Therefore, AGGF1 protein therapy may be a new way to treat patients with skeletal muscle atrophy [50].

Melatonin is an endogenous substance secreted by the pineal gland, which can increase autophagy through the cGAS-STING-TBK and AMPK/FoXO3a signaling pathways, thereby improving oxidative stress and inflammation [95, 96]. The antioxidant effect of melatonin can also be mediated by mitochondria [97]. Mitochondria are an important site for ROS production, and melatonin can protect mitochondrial structure from oxidative stress by regulating glutathione peroxidase (GPx) and glutathione reductase (GRd) to maintain the reduced state of glutathione in mitochondria [98]. Pax7 acetylation regulates skeletal muscle satellite cells self-renewal and muscle stem cell differentiation potential [99]. Melatonin increases Paired box(Pax7) expression to accelerate skeletal muscle differentiation, thereby rapidly rescuing muscle injury[100]. Therefore, melatonin can be used as an important therapeutic target for muscle injury repair. In addition, in PD patients, melatonin can improve neuroinflammation by inhibiting signal transducer and activator of transcription (STAT)-related proinflammatory microglial polarization, providing neuroprotection in PD patients[101]. At the same time, melatonin has potential therapeutic value in improving patients' sleep[102]. Therefore, melatonin supplementation may have certain benefits in the treatment of PD patients with sarcopenia.

Androgen supplementation has been observed clinically to exert anabolic effects, enhance muscle strength, and increase muscle size [54]. Testosterone can promote muscle fiber regeneration and repair by activating IGF-1 level in muscle satellite cells. Binding of IGF-1 to its receptor activates PI3K and Akt, which activate mammalian target of rapamycin (mTOR), thereby promoting muscle protein synthesis [79]. Androgens may also maintain mitochondrial mass by inducing mitochondrial biogenesis and inhibiting autophagy. In addition, testosterone may protect the mitochondrial respiratory chain from oxidative damage and maintain normal oxidative phosphorylation function as found in a large number of animal tests [103-105]. However, no studies of testosterone supplementation have specifically focused on PD patients with sarcopenia. Therefore, the efficacy and safety of supplemental testosterone therapy in PD patients with sarcopenia remain to be

determined [106].

Estrogens, especially estradiol, play a key role in the protection of muscle health in older women. Postmenopausal skeletal muscle mass loss is reversible with estradiol hormone replacement therapy. At the same time, estrogen replacement therapy can also significantly increase the number of muscle satellite cells and improve motor capacity and muscle strength [56]. At the same time, estrogen replacement therapy can also significantly increase the number of muscle satellite cells and improve motor capacity and muscle strength. From the genomic pathway, estrogen promotes mitochondrial biogenesis and ATP production by increasing the expression of PGC-1 and downstream target genes through estrogen receptor α (ERα) and Erβ. From non-genomic pathways, ERα and G protein-coupled estrogen receptor (GPER) enhance mitochondrial respiration and ATP production through PKA-mediated 17β-estradiol [61]. However, estrogen replacement therapy has not been widely accepted as an effective treatment for PD with sarcopenia [107].

Spermidine, a naturally occurring polyamine, has received much attention due to its potential autophagy induction mechanism and is a good target for the prevention and treatment of sarcopenia [47]. The researchers found that spermidine can promote autophagy through activation of the (AMPK)/p27Kip1 and SIRT1/FoXO3a pathways, inducing the proliferation of muscle satellite cells and muscle regeneration [108, 109]. In addition to reducing markers of oxidative damage and preserving mitochondrial function, spermidine has anti-inflammatory properties, Its anti-inflammatory properties are through inhibiting the accumulation of ROS, reducing the expression level of tumor necrosis factor-α (TNF-α), inhibiting the nuclear translocation of NF-κb p65 subunit, and inhibiting the expression of IL-18 and IL-1β[110]. In addition, spermidine has been found to have a potential neuroprotective effect against degenerative changes in PD through its antioxidant and anti-inflammatory properties in animal studies of PD. It rescued neurons in the substantia nigra pars compacta (SNpc) of the midbrain and striatal nerve endings while reducing oxidative stress, neuroinflammation and restoring striatal neurochemistry [111].

Conclusion

Loss of muscle mass and strength as well as neurodegenerative changes are inevitable processes during human aging. Sarcopenia and PD are common diseases in the elderly, and the combination of the two is closely related to falls, fractures, frailty, and even death. At the same time. The progressive loss of function associated with sarcopenia

may ultimately contribute to the neurodegenerative process of PD. Therefore, active detection, diagnosis and appropriate management of PD with sarcopenia are essential. Early screening, detection, and treatment of sarcopenia may serve as a potential protective measure against the decline in strength and physical function that may occur in PD patients as the disease progresses. More and more experts and scholars believe that exercise and nutrition therapy are particularly important for the improvement of patients' condition and life treatment. Although a variety of drugs have been found to be beneficial in the treatment of PD with sarcopenia, there is no specific drug for the disease at present, and a variety of basic and clinical trials need to be carried out in the future.

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911 Table 1 Diagnostic methods and cut-off values in the latest consensus

Consensus	Muscle strength (grip strength: kg)	Muscle mass	Physical function
IWGS[112]	—	DXA-ALMI： M<7.23 kg/m2，F<5.67kg/m2	step speed＜ 1.0 m/s
FNIH[113]	M＜26 F＜16	DXA-ASM/BMI ： M<0.789，F<0.512 ALM(kg):M<19.75 ，F<15.02	step speed＜ 0.8 m/s
EWGSOP，2018[1]	M＜27 F＜16	DXA-ASMI ： M<7.0 kg/m^2，F<6.0 kg/m^2	step speed＜ 0.8 m/s or SPPB ≤ 8 points orTUG ≥ 20 s or The 400-m walk was not completed or≥ 6 min or5STS＞15 s
AWGS，2019[16]	M＜28 F＜18	DXA-ASMI: M<7.0 kg/m^2，F<5.4 kg/m^2 BIA-ASMI: M<7.0 kg/m2，F<5.7 kg/m2	step speed＜ 1.0 m/s or SPPB ≤ 9 points or5STS＞12 s

912 ASM: appendicular skeletal muscle mass; ALM: appendicular skeletal muscle mass;
913 ASMI: appendicular skeletal muscle mass index;ALMI: appendicular skeletal muscle
914 mass index