Rehabilitation Management for Sarcopenia in Chronic Obstructive Pulmonary Disease: A Literature Review

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Abstract
Chronic obstructive pulmonary disease (COPD) is a prevalent and debilitating chronic respiratory condition that not only affects the lungs but has far-reaching systemic consequences; one such consequence is the heightened risk of developing sarcopenia, a condition characterized by progressive loss of skeletal muscle mass and strength. Recent studies have highlighted the significant prevalence of sarcopenia among COPD patients, with rates ranging from 7.9% to 66.7%. This association underscores the importance of early identification and intervention to mitigate the adverse outcomes related to both conditions. Managing COPD patients with sarcopenia is fraught with challenges, primarily due to the multifaceted nature of both conditions. Sarcopenia exacerbates the decline in respiratory function and physical performance in COPD patients, complicating treatment and management strategies. The complexity is further amplified by the need for personalized treatment plans that address these conditions' pulmonary and musculoskeletal aspects. Precise assessment and re-evaluation are essential to ensure optimal outcomes and enhance physical and functional well-being. Rehabilitation for COPD patients with sarcopenia involves a multidisciplinary approach, focusing on exercise training, nutritional support, and pulmonary interventions. Pulmonary rehabilitation programs, tailored to individual patient needs and capabilities, have shown promise in improving exercise capacity, functional performance, and overall health status, thereby enhancing the quality of life for these patients. In this literature review, we will discuss the elevated risk of sarcopenia in COPD patients, highlight the significance of rehabilitation management, and emphasize the pivotal role of precise assessment and re-evaluation in optimizing the care provided to this population.

Keywords: COPD, exercise, rehabilitation, sarcopenia
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a primary global health concern and is one of the leading causes of death worldwide, particularly in developing countries. Although a preventable disease, COPD is the third leading cause of death globally, with 90% of mortality occurring in developing countries. The most common cause of COPD development in middle age is chronic smoking.\textsuperscript{1,2}

COPD is characterized by persistent airflow limitation primarily due to inflammation of the respiratory tract and lungs caused by exposure to harmful gases or particles. Critical symptoms of COPD include chronic respiratory distress, such as dyspnea, chronic cough, sputum production, and exacerbations.\textsuperscript{1,2}

Chronic obstructive pulmonary disease not only affects the respiratory system but also has systemic implications, often coexisting with other medical conditions, such as cardiovascular disease, metabolic syndrome, osteoporosis, depression, and anxiety. Moreover, COPD leads to skeletal muscle dysfunction, resulting in sarcopenia and cellular abnormalities. Sarcopenia is characterized by decreased muscle mass and/or impaired muscle function, often accompanied by symptoms such as fatigue and reduced physical activity.\textsuperscript{3}

Sarcopenia occurs at a notably high rate among individuals with COPD. The prevalence of sarcopenia in patients with COPD varies significantly across different studies, primarily due to differences in the populations studied, the methods used to assess sarcopenia, and the definitions of sarcopenia used. A systematic review and meta-analysis found that the prevalence of sarcopenia in COPD patients ranged from 7.9% to 66.7%, with an overall prevalence of 21.6%.\textsuperscript{3}

The occurrence of sarcopenia linked to COPD is affected by various risk factors, which include the severity of lung disease and other clinical conditions, such as systemic inflammation, oxidative stress, smoking, low oxygen levels, reduced physical activity over time, and malnutrition.\textsuperscript{3}

The interaction between sarcopenia severity and respiratory dysfunction may be critical for the prognosis or progression of COPD. This Literature Review aims to provide insights into the current knowledge regarding Sarcopenia in COPD. Based on the recent research findings, it explores the pathogenesis mechanisms, contributing factors, clinical implications, assessment methods, and management strategies for COPD patients, focusing on rehabilitation.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease that can be prevented and treated. It causes persistent airflow limitation that usually worsens over time, excessive chronic inflammation of the airways and lung parenchyma due to exposure to harmful gases or particles, and chronic respiratory distress such as shortness of breath,
coughing, sputum production, and flare-ups.\textsuperscript{1,2}

Significant systemic consequences are associated with COPD, indicating the existence of underlying concomitant diseases. The impact of COPD on each individual varies according to the severity of symptoms, primarily dyspnea and decreased exercise capacity, systemic implications, and other concurrent conditions.\textsuperscript{1}

Several factors contribute to COPD pathological changes: structural changes such as an increase in goblet cells and enlargement of submucosal glands contribute to excessive mucus production, metaplasia of squamous epithelial cells, alveolar wall degradation and death of epithelial and endothelial cells, manifest as emphysema.\textsuperscript{2}

In addition, structural abnormalities in pulmonary blood arteries, such as intimal thickening, endothelial cell dysfunction, and smooth muscle hypertrophy, contribute to pulmonary hypertension.\textsuperscript{2,4} Diaphragm dysfunction in individuals with COPD is a consequence of dynamic hyperinflammation, leading to mechanical losses and weakness. During exacerbations, this weakness is driven by increased numbers of lung inflammatory cells, oxidative stress-induced diaphragmatic damage, ongoing diaphragm remodeling processes, the persistence of hyperinflammatory areas that disrupt diaphragmatic performance, and dynamic changes in mitochondrial function.\textsuperscript{4}

COPD Implications

The COPD exacerbation and episode of hospitalization have various non-pulmonary consequences due to medical approaches. Systemic inflammation, high doses or prolonged use of corticosteroids, oxidative stress, hypoxia, and hypercapnia could cause further cardiac disease, impaired glucose control, and other complications.\textsuperscript{5}

During hospitalization, patients' immobility, imbalance of catabolic-anabolic metabolism, and reduced dietary intake may lead to sarcopenia, malnutrition, rapid deconditioning, osteoporosis, cognitive impairment, and, at last, self-efficacy and the patient's confidence. The above has a more significant impact, such as increased readmission, disability, and even death.\textsuperscript{5}

Multimorbidity in patients with COPD is frequently associated with cardiovascular disease, metabolic syndrome, osteoporosis, depression, and anxiety. Additionally, COPD exerts a significant impact on extrapulmonary manifestations, referred to as systemic effects of COPD. These systemic effects encompass weight loss, nutritional abnormalities, and skeletal muscle dysfunction.\textsuperscript{1,4}

In COPD, there is a 2-3 times higher risk of cardiovascular disease; even mild COPD contributes significantly to the pathobiology of cardiovascular abnormalities.\textsuperscript{6} Skeletal muscle dysfunction is characterized by sarcopenia and cellular function abnormalities. The underlying mechanisms of systemic effects need further investigation, as they are multifactorial, involving factors such as
inactivity, an unhealthy diet, inflammation, and hypoxia. These factors contribute to exercise intolerance and suboptimal health status in COPD patients. Therefore, addressing systemic effects is crucial to reduce morbidity in COPD patients, and it should be assessed and managed based on individual patient conditions.¹,6

Nutritional abnormalities are common among individuals with COPD, and these abnormalities involve various aspects of their dietary and metabolic profiles. This includes changes in caloric intake, basal metabolic rate (BMR), intermediary metabolism, and body composition. Unexplained weight loss is a noteworthy aspect of COPD-related nutritional abnormalities. Up to 50 percent of persons with severe COPD and persistent respiratory failure are susceptible to this phenomenon. Surprisingly, about 10 to 15 percent of people with mild to moderate COPD also have this condition. Loss of skeletal muscle mass, accompanied by a fall in fat mass, is a significant cause of weight loss in COPD patients.⁶

Exception of patients experiencing disease exacerbations: these nutritional abnormalities are not typically related to a lower caloric intake. Instead, COPD patients generally have a greater basal metabolic rate (BMR), which might contribute to weight loss. This higher BMR can be caused by many causes, including elevated respiratory effort, the use of commonly prescribed COPD medications (such as 2-agonists), systemic inflammation, and tissue hypoxia.⁶

In conclusion, nutritional abnormalities and unexplained weight loss are essential concerns in COPD patients, as they arise from complicated interactions involving metabolic and inflammatory variables, as opposed to calorie restriction alone. Understanding these mechanisms is necessary to develop practical solutions to treat dietary difficulties and weight loss in COPD patients.⁶

Skeletal muscle dysfunction in patients with COPD is characterized by specific anatomical changes, such as quadriceps weakness, atrophy, and a shift in muscle fiber type towards type II fibers. Functional changes, including reduced muscle strength, endurance, and enzymatic activity, are also prominent features of this dysfunction. Skeletal muscle dysfunction significantly contributes to limitations in exercise capacity and decreased quality of life for individuals with COPD.⁶,⁷

Notably, COPD patients’ respiratory muscles, particularly the diaphragm, differ structurally and functionally from skeletal muscles. This disparity could be the result of different working conditions for these muscles. In COPD patients, lean muscles are often underused, whereas the diaphragm continuously struggles against increasing strain. Several factors play a role in the development of skeletal muscle dysfunction in COPD patients, including a sedentary lifestyle, tissue hypoxia, and systemic inflammation.⁶

Systemic inflammation, influenced by cytokines like TNF-α, oxidative stress, and nitrosative stress, can lead to muscle
dysfunction, atrophy, and apoptosis. COPD patients exhibit elevated circulating levels of these cytokines and inflammatory cells. Muscle atrophy and weakness are found in 30-40% of COPD patients. Those with muscle wasting and fault tend to be sedentary and may become bedridden, exacerbating lung function and the overall COPD condition.

Sarcopenic obesity (SO) is prevalent among patients with COPD, presenting a significant comorbidity that complicates the clinical outcomes of these patients. The condition of sarcopenic obesity combines the characteristics of sarcopenia (loss of skeletal muscle mass and function) and obesity (excess body fat accumulation), each of which independently affects the health status of COPD patients.

The pathogenesis of sarcopenic obesity in patients with COPD is multifaceted, involving a complex interplay of systemic inflammation, muscle dysfunction, and metabolic disturbances. The abnormal expression of adipocytokines, such as resistin, is significant in the pathogenesis of sarcopenic obesity in COPD. Resistin plays a crucial role in lipometabolism and has pro-inflammatory effects, which contribute to the complex inflammatory response observed in COPD patients with sarcopenic obesity.

SARCOPENIA IN PATIENTS WITH COPD

In 1989, Rosenberg first described age-related alterations in muscles and pioneered "sarcopenia" to refer to the age-related loss of muscle mass. The term sarcopenia has developed to incorporate muscular atrophy and muscle function. Sarcopenia is the age-related decrease of skeletal muscle mass, which raises the risk of physical disability, deteriorating health, and mortality. It is recognized as a clinical syndrome that includes physical inactivity, malnutrition, and chronic diseases.

The loss of muscle mass in sarcopenia is generally attributed to a combination of muscle atrophy and muscle cell death. At the molecular level, there are changes in protein synthesis and degradation in sarcopenia. Sarcopenia affects both respiratory and non-respiratory muscles. It is influenced by systemic inflammation, oxidative stress, hypoxia, hypercapnia, protein synthesis, catabolic imbalance, nutritional changes, smoking, endocrine dysfunction, aging, and medications like steroids.

Each of these factors, either individually or collectively, leads to muscle mass reduction, cross-sectional area reduction, decreased bioenergetic muscle metabolism (related to fiber type ratio, mitochondrial activity, and muscle blood flow availability), impaired muscle repair, and regeneration mechanisms, along with anatomical and functional pathology (such as apoptosis). These combined effects result in decreased muscle performance. Ongoing research continues to investigate the molecular mechanisms involved in sarcopenia. Reduced muscle mass and impaired muscle function are pivotal components of sarcopenia, initially
characterized as a multifaceted geriatric syndrome. However, it is now widely acknowledged that muscle impairment can be attributed to various diseases, extending beyond age-related factors. The onset of sarcopenia is multifactorial, involving neurological factors related to motor neuron loss, endocrine factors such as reduced hormone expression (e.g., testosterone and growth hormone), motor unit loss, nutrition, and sedentary lifestyle changes. Inactivity is often accompanied by an imbalance in high saturated fat intake, leading to increased fat deposition in adipose tissue, the liver, and muscles.

In the context of COPD patients, skeletal muscle dysfunction is an independent adverse prognostic factor for lung function. Importantly, extrapulmonary manifestations play a substantial role in the decline of functional capacity among individuals with COPD, and these functional impairments are closely linked to muscle weakness and weight loss.

Sarcopenia in COPD has a detrimental impact, reducing the quality of life and increasing hospitalization rates, mortality, and financial burdens. Recognizing this broader perspective, the European Working Group of Sarcopenia in Older People (EWGSOP2) has underscored the significance of differentiating between "secondary sarcopenia," influenced by factors other than aging, and "primary sarcopenia," which is primarily age-related. Notably, sarcopenia can be induced by underlying diseases such as COPD or other conditions characterized by chronic inflammation.

Based on a Systematic Review and Meta-Analysis by Benz et al, the prevalence of sarcopenia in COPD is 21.6%, with varying rates of 8% in the general population, 21% in clinic-based studies, and 63% among COPD patients in nursing homes. According to a cross-sectional study conducted by Costa et al in 2015 on the relationship between COPD severity and prognosis, the prevalence of sarcopenia was found to be 39.6% (36 out of 91 patients).

Sarcopenia was not associated with GOLD stage or FEV1 results. However, it was more prevalent in COPD patients with Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) index in quartiles 3 and 4 compared to quartiles 1 or 2. Multivariate analysis indicated a significant association between BODE quartiles and sarcopenia, irrespective of age, gender, smoking status, and GOLD stage.

**Sarcopenia Pathogenesis in COPD patients**

Sarcopenia in COPD is a result of chronic systemic inflammation. Various molecular pathways contribute to its processes, such as inflammatory mediators, satellite cells, neuronal processes, and hypoxemia. Other mechanisms like muscle dystrophy, glucocorticoids, medications, and disease also contribute to the development of sarcopenia in COPD patients. In patients experiencing muscle decline, it shows
increased levels of TNF-α and IL-6, which are negatively correlated with grip strength and skeletal muscle mass index.\textsuperscript{13}

The immune system also plays a crucial role in skeletal muscle regeneration; however, the diminished muscle regenerative capacity found in sarcopenia is caused by local inflammation mechanisms that trigger changes in neurohormonal responses, thus resulting in an imbalance between protein synthesis and degradation, pro-inflammatory cytokines, such. The imbalance between pro- and anti-inflammatory factors results in chronic low-grade pro-inflammatory states progressively damaging muscles.\textsuperscript{12} Inflammation also influences skeletal muscle dysfunction through oxidative stress and muscle cell apoptosis.\textsuperscript{13}

Aging processes are associated with increased pro-inflammatory cytokines, leading to increased production of acute-phase reactive proteins, immune responses, and immune-senescence or inflammation. As individuals age, the activation of satellite cells significantly decreases or may even halt, influenced by various factors. Moreover, older individuals require more significant stimuli, such as muscle fiber stretching, to activate satellite cells. Consequently, advancing age is closely associated with a notable reduction in actively functioning satellite cells, which can impact muscle regeneration and overall muscle health.\textsuperscript{12}

Oxidative stress, a critical factor in diseases like COPD, significantly affects skeletal muscle. Sources include lack of oxygen, inflammation, smoking, environmental pollutants, and increased respiratory rates. These reactive oxygen/nitrogen species ROS/RNS) cause structural and functional alterations, leading to sarcopenia. Understanding this relationship is crucial for developing effective therapeutic strategies to manage sarcopenia in COPD patients.\textsuperscript{12,13} Muscle contraction involves brain structures and neurotrophic factors. Brain-derived neurotrophic factor (BDNF), a critical neurotrophic factor, is crucial in muscle fiber metabolism and DNA repair. It is released during skeletal muscle contractions, improving lipid metabolism and muscle fiber function.\textsuperscript{12}

Increased physical activity boosts BDNF production, maintaining the central nervous system and skeletal muscle homeostasis. Another neurotrophic factor, insulin-like growth factor I (IGF-1), is essential for protein synthesis and binds to the IGF receptor, preventing protein degradation.\textsuperscript{15} These mechanisms are crucial for muscle health and the potential consequences of aging.

The pathomechanism of sarcopenia is closely intertwined with reduced physical activity, creating a detrimental cycle of muscle deterioration. Hyperinflation and the sensation of breathlessness in COPD patients can lead to reduced physical activity. Skeletal muscle disuse can trigger various adaptive changes, including decreased type I fibers and oxidative capacity, muscle fiber atrophy, and muscle capillary density. These changes result in decreased muscle endurance and strength. The reduced strength and endurance of
muscles further limit the mobility of COPD patients, exacerbating problems.\textsuperscript{13}

A study found that sedentary healthy individuals have fewer type I muscle fibers in their vastus lateralis muscle than active, healthy individuals. This decrease in muscle endurance is attributed to atrophy of disused muscles, which leads to faster proteolysis and reduced protein synthesis.\textsuperscript{13}

Patients with sarcopenia or COPD generally experience a reduction in physical activity; moreover, sarcopenia in COPD patients. All of these ultimately lead to muscle atrophy. Protein breakdown in COPD patients is often caused by a decrease in appetite, age-related anorexia, and muscle-related issues, thus resulting in inadequate energy intake. The breakdown of the protein process thus leads to skeletal muscle atrophy, reduced exercise tolerance, and a lower quality of life for the patients. As malnutrition is prevalent among the majority of COPD patients, nutritional status plays a crucial role in the development of sarcopenia.\textsuperscript{13}

**Clinical Impact of Sarcopenia in COPD Patients**

Deconditioning due to low activity is a primary cause of significant muscle dysfunction. In COPD, the most dominant muscle atrophy occurs in the leg muscles, particularly the thigh muscles, compared to other muscle groups. In severe COPD, there is a shift from type I to type IIx muscle fibers, which become less efficient in energy output, requiring higher oxygen levels during submaximal workload. Systemic oxidative stress is correlated with quadriceps muscle endurance in severe COPD patients.\textsuperscript{11}

In individuals with hypoxemia, there is a higher level of oxidative stress in extremity muscles, leading to decreased quadriceps function. The strength of the quadriceps muscles in COPD patients is typically 20-30\% lower than in the average population.\textsuperscript{11}

Consequently, COPD patients exhibit significantly lower quadriceps endurance and strength. Many COPD patients complain of leg fatigue, which often leads to exercise termination before experiencing shortness of breath. Weakness in the quadriceps muscles is frequently observed after acute COPD exacerbations, and it takes approximately three months of treatment to restore muscle strength.\textsuperscript{11}

**Sarcopenia Assessment**

Early detection of sarcopenia in COPD is crucial, given its therapeutic implications for pulmonary rehabilitation and the management of respiratory failure in COPD patients.\textsuperscript{14} The Asian Working Group for Sarcopenia (AWGS) 2019 consensus provides a comprehensive approach to diagnosing sarcopenia, which includes assessments of muscle strength, muscle mass, and physical performance. AWGS 2019 consensus defines sarcopenia as losing muscle mass due to aging, low muscle strength, and reduced physical performance.\textsuperscript{16}

The Asian Working Group for Sarcopenia determines cut-off values for each diagnostic component based on Asian
research findings. Although sarcopenic characteristics can be found in younger individuals, further investigation of the underlying pathophysiology is needed before diagnosing it as sarcopenia. AWGS supports the early identification of at-risk individuals to enable precise interventions. In the AWGS 2019 guidelines, the diagnosis of sarcopenia requires measuring muscle quantity and quality. It defines severe sarcopenia as having low muscle mass, low muscle strength, and low physical performance.\textsuperscript{16}

Handgrip strength assessment remains recommended for evaluating muscle strength. Asia’s most commonly used handgrip dynamometers are the spring-type dynamometer (Smedley) and hydraulic-type (Jamar). AWGS 2019 suggests that muscle strength measurements for sarcopenia evaluation can utilize any equipment if it follows the standardized protocol for each specific model. The proposed method for assessing handgrip strength involves obtaining the highest result from at least two trials using both hands or the dominant hand with maximal isometric contraction effort.\textsuperscript{16}

There are various types of physical performance tests: the Short Physical Performance Battery (SPPB), assesses lower-extremity function through tasks like walking, balancing, and chair stands. The usual gait speed test typically involves measuring the time it takes for an individual to walk a specified distance, such as 4 meters, and calculating the speed in meters per second (m/s).\textsuperscript{18}
Table 1. Assessment tools recommended by AWGS 2019 for sarcopenia\textsuperscript{16}

<table>
<thead>
<tr>
<th>Assessment Component</th>
<th>Tool/Method</th>
<th>AWGS 2019 Cut-off Values</th>
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<tbody>
<tr>
<td>Muscle Strength</td>
<td>Handgrip Strength Test</td>
<td>Men: &lt;28 kg; Women: &lt;18 kg</td>
</tr>
<tr>
<td>Muscle Mass</td>
<td>• Dual-energy X-ray Absorptiometry (DXA)</td>
<td>Men: &lt;7.0 kg/m(^2); Women: &lt;5.4 kg/m(^2)</td>
</tr>
<tr>
<td></td>
<td>• Bioelectrical Impedance Analysis (BIA)</td>
<td>Men: &lt;7.0 kg/m(^2); Women: &lt;5.4 kg/m(^2)</td>
</tr>
<tr>
<td>Physical Performance</td>
<td>• Usual Gait Speed</td>
<td>&lt;1.0 m/s</td>
</tr>
<tr>
<td></td>
<td>• Short Physical Performance Battery (SPPB)</td>
<td>Score &lt;9</td>
</tr>
<tr>
<td></td>
<td>• Timed Up and Go Test (TUG)</td>
<td>≥12 seconds</td>
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The 6-minute walk test measures the distance an individual can walk over a total of six minutes on a hard, flat surface. It assesses the aerobic capacity and endurance of an individual. Stair-climb power test evaluates leg muscle power by measuring the time it takes to ascend a set number of stairs. Timed-up-and-go test assesses mobility, balance, walking ability, and fall risk in older adults by timing how long it takes an individual to stand up from a chair, walk a short distance, turn around, walk back to the chair, and sit down.\textsuperscript{18}

The 5-time chair stand test (5-CST) measures lower limb muscle strength by timing how quickly an individual can rise from a chair and sit down five times without using their arms. Poor performance in the 5-CST indicates reduced lower limb muscle strength and has been recommended for use in the initial assessment of sarcopenia.\textsuperscript{18}

REHABILITATION MANAGEMENT SARCOPENIA IN COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) includes physical activity as a non-pharmacological intervention in managing stable COPD.\textsuperscript{1} GOLD emphasizes that non-pharmacological management complements pharmacological treatment and is integral to comprehensive COPD management.\textsuperscript{16} Besides that, AWGS recommends the importance of intervening in sarcopenia in patients with or without underlying clinical conditions.\textsuperscript{12}

To date, there is no curative therapy for sarcopenia, and the current management strategy aims to delay its onset and reduce symptoms, primarily through physical activity. Sedentary lifestyles in elderly patients lead to skeletal muscle inactivity, accelerating muscle strength loss and muscle atrophy. By controlling various variables, including oxidative stress, neuronal dysfunction, and inflammation, exercise can offset the detrimental effects that contribute to sarcopenia.\textsuperscript{12}

The physical medicine and rehabilitation management benefits for COPD patients with sarcopenia include improvements in skeletal muscle mass and strength, which can halt or even reverse
the progression of muscle loss. Rehabilitation can also alleviate the disease burden and improve the quality of life for these patients. Pulmonary rehabilitation has been shown to reverse sarcopenia in patients with low skeletal muscle mass and improve exercise capacity, functional performance, limb strength, and health status.\(^8\)

As part of a rehabilitation program, regular exercises are an effective strategy for protecting against sarcopenia in COPD patients, as they can increase muscle mass and strength. Additionally, nutritional supplements combined with exercise have been found to improve the performance of patients with coexisting COPD and sarcopenia. Pulmonary rehabilitation (PR) programs for COPD patients with sarcopenia can vary in duration and intensity, tailored to the individual's capabilities, and may include both aerobic and resistance training components.\(^8\)

**Exercise**

Pulmonary rehabilitation in COPD patients has demonstrated its effectiveness, offering tangible benefits supported by high-quality scientific evidence. The primary objective of pulmonary rehabilitation is to enhance exercise capacity, alleviate breathlessness, and improve the quality of life for patients. Pulmonary rehabilitation represents an integrated multidisciplinary management program encompassing exercise, education, behavior modification, and nutritional therapy.\(^11,19\)

Exercise is recognized as one of the most productive approaches to addressing sarcopenia. EWGSOP endorses exercise as the primary intervention for sarcopenia, intending to enhance physical performance, strength, and muscle mass.\(^11\)

**Exercise-induced molecular remodeling**

Sarcopenia exercise programs comprise multimodality, including strength-resistance, aerobic exercise, balance, and flexibility training, in which strength training stands as the frontline intervention for managing sarcopenia.\(^20\) Exercise benefits sarcopenia patients through multiple molecular pathways, including antioxidant alteration, reduction of myostatin expression, activation of satellite cells, and positive effects on telomere length, ultimately preserving muscle strength and function. Physical exercise induces alterations in antioxidant enzyme levels in acute and long-term scenarios.\(^12\)

These changes are prompted by ROS generated during exercise, pivotal in muscle adaptation to decelerate sarcopenia. Consequently, post-exercise ROS in muscle cells can act as numerous genes' activators or suppressors. Skeletal muscles can adapt to specific stimuli or stressors induced by concentric or eccentric muscle contractions, stretching, or contraction.\(^12\) Strength or resistance training provides relief to the issues of muscular atrophy and weakness, which have been fundamental components of sarcopenia.\(^21\) Not only does strength training improve muscle strength and
quality of life, but also beneficial to increase the exercise capacity of COPD patients.\textsuperscript{21}

Furthermore, to boost muscle strength efficiently, it is recommended to do multi-joint exercises.\textsuperscript{21} Resistance training is less aerobic and oxidative than aerobic exercise, as it increases nitric oxide levels and NO synthase (NOS), indirectly shielding muscles from pro-oxidant effects. This promotes antioxidant defenses and reduces inflammatory pathways during exercise. This evidence underscores the foundation and management of muscle abnormalities resulting from aging, emphasizing the importance of physical exercise and nutritional intake.\textsuperscript{12}

Exercise can be a double-edged sword for sarcopenia patients. While it can help improve muscle strength and function, it may also increase myostatin expression in muscle fiber, a factor associated with muscle wasting. In sarcopenia exercise, the increase in myostatin expression is often accompanied by a parallel enhancement in the activation and proliferation of satellite cells, representing a complex interplay within the muscle microenvironment.\textsuperscript{12}

The activation of satellite cells is triggered by nitric oxide (NO) produced by NOS in quadriceps muscles during active but not passive exercise. Resistance training enhances the activation and proliferation of satellite cells. There is an increase in satellite cells in skeletal muscles by 19\% after 30 days of resistance training and 31\% after 90 days of resistance training.\textsuperscript{12}

Changes in satellite cells following adaptation to exercise are associated with decreased oxygen levels in muscle cells and increased vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), which can influence satellite cell proliferation induced by resistance training. In addition, regular resistance training and moderate oxidative stress positively affect telomere length in leukocytes and skeletal muscles. There is strong evidence that satellite cell activity is crucial in delaying sarcopenia as a response to exercise adaptation, maintaining muscle strength and functionality.\textsuperscript{12}

**Skeletal Muscle Adaptation in Resistance Exercise**

Exercise induces the remodeling of skeletal muscles, supported by acute and chronic genetic alterations and protein production. Skeletal muscles are highly plastic tissues capable of adapting to minor nutrition and contractile activity alterations. Resistance exercise significantly stimulates the rate of muscle protein synthesis (MPS) with only minimal impact on muscle protein breakdown (MPB) rates.\textsuperscript{22}

Combining resistance exercise with protein intake results in an increased rate of MPS in skeletal muscle proteins, ultimately leading to muscle hypertrophy. Dynamic stimulation of skeletal muscles with low-intensity, repetitive, and prolonged loads (as seen in endurance training) enhances the expression of mitochondrial genes, proteins, and mitochondrial content, shifting towards an oxidative phenotype and increasing resistance to fatigue.\textsuperscript{22}
Resistance exercise stimulates gene transcription and accelerates the synthesis of new muscle proteins. During prolonged exercise, a transcriptional response, protein synthesis response, and proteomic changes result in muscle hypertrophy and an oxidative phenotype. The biological basis of exercise-induced skeletal muscle phenotype changes lies in the repeated stimulation of increased mRNA expression, leading to enhanced protein translation and adaptive alterations in muscle protein content.\textsuperscript{22}

One gene transcription induced by resistance exercises was found in the mechanistic target of rapamycin complex 1 (mTORC1). Its activation enhances muscle protein synthesis through the downstream activation of proteins such as ribosomal protein 70-kDa S6 kinase 1 (p70S6K1) and 4E-binding protein-1 (4EBP1), which initiate ribosome binding to mRNA for protein synthesis initiation. Therefore, resistance exercise stimulates mTORC1 activity, leading to increased rates of myofibrillar protein synthesis through enhanced translation efficiency (protein synthesized per unit mRNA) and translation capacity (ribosome quantity).\textsuperscript{22}

**Endurance training**

Exercise-induced mitochondrial biogenesis is a characteristic of endurance training. It is supported by increased regulation of mitochondria and coordinated nuclear transcription encoding proteins involved in the electron transport chain and fatty acid metabolism. These transcriptional processes include peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, nuclear respiratory factors (NRFs), and mitochondrial transcription factor A (TFAM). Endurance training over an extended period elevates mRNA expression of PGC-1α. Endurance exercise results in highly coordinated mitochondrial adaptations (from mRNA to protein) that are time-dependent (ranging from hours to days).\textsuperscript{22}

**Impact of exercise repetitions**

When combined with protein intake, skeletal muscles enter a positive protein balance shortly after exercise. Changes in the cross-sectional area (CSA) of skeletal muscle fibers are only minimally detected through photochromic staining after 6-7 weeks of exercise. An increase in total RNA and 45S pre-rRNA occurs after 3 weeks and 6 weeks of resistance exercise, with this expression returning to baseline levels after 2 weeks of resistance exercise.\textsuperscript{22}

Resistance exercise over 20 weeks shows that individuals with the highest muscle hypertrophy display increased rRNA expression. Furthermore, muscle protein synthesis (MPS) increases within a few hours after resistance exercise and skeletal muscles remain responsive to anabolic influences 24-48 hours after protein intake. The early-phase elevation in MPS during post-resistance exercise recovery indicates the remodeling of contractile and structural proteins.\textsuperscript{22}

Resistance exercise induces skeletal muscle contractions using external resistance, such as dumbbells, elastic therapy bands, and the patient's body
weight. In general, resistance training can begin with a load of 50-60% of the one-repetition maximum (1RM) for 12-15 repetitions.

Evaluation of improvement in muscle strength should be conducted routinely; therefore, the exercise intensity can be gradually increased with a frequency of 1 to 3 sets per day. Resistance training, especially for thigh muscles, is crucial for daily activities such as standing and walking, and weakness in thigh muscles can lead to physical inactivity. Although intensive resistance training in elderly patients has proven effective in enhancing muscle function and mass, it is recommended to gradually increase the intensity of progressive overload training to prevent musculoskeletal injuries.

Intensive resistance training in elderly patients has proven effective in enhancing muscle function and mass. However, it is recommended to gradually increase the intensity of progressive overload training to prevent musculoskeletal injuries. The effects of resistance training in older patients include muscle hypertrophy, increased muscle strength, and improved physical performance. High-intensity resistance training is more effective for sarcopenia than home-based exercises or exercises with light resistance.

However, a 6-month home-based exercise program that combines walking and resistance exercises for the lower extremities (such as squats, single-leg standing, and heel raises) is efficacious in improving maximum walking speed and muscle strength in patients aged 60 or older with sarcopenia or low muscle mass.

Resistance training is recommended 2 to 3 days per week, combined with aerobic exercise to maintain cardiovascular function. It is advised to incorporate 1 day of rest and mental recovery. Resistance and endurance exercises should be adapted to each patient’s recommendations and exercise protocols, considering motor limitations, intensity, and duration.

The recommendations provided by Cruz-Jentoft et al. suggest supervised resistance training or exercise programs for sedentary or frail patients. The intervention should last at least 3 months or longer to achieve significant clinical outcomes, particularly in muscle strength and physical performance. Although Cruz-Jentoft et al. found that resistance exercise increases muscle strength and physical performance but does not significantly affect muscle mass.

Aerobic or endurance exercise prevents muscle loss and is effective with resistance training. Endurance exercise improves hyperinflammation conditions induced by exercise. It reduces exertional dyspnea, heart rate recovery, and muscle dysfunction in COPD patients.

Common exercise modalities include walking on the ground or on a treadmill and static cycling. Patients with COPD often experience breathlessness and quad muscle fatigue after cycling or walking; ground walking could enhance walking capacity. Upper extremity exercises are
also advised for COPD patients, such as aerobic arm cycle ergometer training targeting muscles like the biceps, triceps, deltoids, latissimus dorsi, and pectoralis.\textsuperscript{21}

Furthermore, balance training is crucial for patients, especially older individuals, to improve postural control.\textsuperscript{11}

One consideration when prescribing exercise for COPD patients is the decreased respiratory function, which then poses a risk for exercise-induced desaturation (EID) in severe and very severe COPD patients with an FEV1 <50%. A SpO2 saturation <90% that remains uncorrected indicates terminating exercise. If EID is identified, adequate oxygenation should be provided during exercise. It is advisable to exercise indoors to prevent exposure to air pollution and fine particles that may trigger acute exacerbations.\textsuperscript{11}

**High-Intensity Interval Exercise**

High-intensity interval exercise (HIIE) improves cardiorespiratory fitness and stimulates mitochondrial biogenesis in muscles. HIIE notably impacts muscle protein remodeling and hypertrophy by increasing muscle protein synthesis (MPS), particularly mitochondrial protein synthesis, and inducing fibrillar protein remodeling.\textsuperscript{22}

An increase in the number of differentiated satellite cells has been observed after HIIE, indicating the role of satellite cells in muscle fiber remodeling. HIIE training enhances the number of satellite cells associated with hybrid muscle fibers, supporting the idea that HIIE plays a role in triggering muscle fiber remodeling.\textsuperscript{22}

**Exercise prescription**

To prescribe exercise for COPD patients with sarcopenia, a comprehensive approach that includes targeted exercise training and aerobic and strengthening exercises, alongside adequate protein and caloric intake and micronutrient management, is recommended.\textsuperscript{8}

The exercise type should be a combination of aerobic and resistance training, starting 3 times per week and aiming for 5 times as tolerated. The intensity should be based on perceived effort, heart rate, and exercise capacity, 4 to 12 weeks, with 60 to 90-minute sessions. This exercise prescription should be personalized to each COPD patient with sarcopenia, considering their current health status, exercise tolerance, and nutritional needs.\textsuperscript{8}

**Exercise Precautions**

Research by Sahin and Naz on the demographic and clinical characteristics of COPD patients who failed to complete an 8-week PR exercise program found that patients with a history of smoking and severe COPD were the most common non-completers, often due to a lack of motivation (49%), transportation problems (23.8%), exacerbations (18.4%), work-related reasons (4.8%), and hospitalization (4.1%). This underscores the importance of healthcare professionals providing clear information and maintaining a positive attitude while interacting with patients.\textsuperscript{24}
ASSSESSMENT METHODS FOR COPD PATIENT EXERCISE

Patient assessment and program outcomes are crucial components of patient exercise programs. It is essential to assess the patient’s condition before starting an exercise regimen, including symptoms, endurance, strength, quality of life, and other relevant factors. These assessments should be conducted before, during, and after exercise to evaluate effectiveness. Breathlessness is the most commonly reported symptom by COPD patients. Identifying and evaluating the patient’s symptoms before, during, and after exercise is vital to guide their exercise regimen.21

NUTRITIONAL THERAPY

Malnutrition increases the risk of weight loss and has implications for the development of sarcopenia. In conditions of calorie deficit, protein becomes the primary source of energy; consequently, a combination of adequate nutritional and additional protein intake. Research has shown a positive correlation between protein intake and muscle mass. A study involving 2,066 elderly patients found that the group with a protein intake of 1.2 g/kg had lower muscle mass loss than the group with an infusion of 0.8 g/kg. The PROT-AGE study group recommends a protein intake of 1.2–1.5 g/kg for elderly individuals with acute or chronic diseases.11

Omega-3, healthy fats, and hydration are also essential for individuals with sarcopenia.20 Significant clinical improvements have been noted in mid-arm circumference, fat-free mass index (FFMI), results of the 6-minute walk test, respiratory muscle strength, and quality of life when providing nutritional supplementation to malnourished COPD patients.11

MEDICATION

Several medications and supplements are known to be beneficial for COPD patients with sarcopenia. Vitamin D plays a crucial role in muscle metabolism, the formation of skeletal muscle mass, and muscle strength. Type II muscle fiber atrophy may occur in cases of vitamin D deficiency. Type II muscle fibers play a role in preventing falls through fast-twitching; therefore, vitamin D supplementation can reduce the risk of falling. Sarcopenic patients with low vitamin D levels (<20 ng/mL based on the 25-hydroxyvitamin D test) should receive vitamin D supplementation. Beta-hydroxy-β-methylbutyrate (HMB) is a metabolite of leucine often used as a nutritional supplement in muscle training. HMB enhances protein synthesis through protective and anti-catabolic effects, stabilizes muscle cell membranes, and reduces proteolytic pathways, lowering sarcopenia. In COPD, HMB is known to prevent muscle loss, with a standard dose of 3 grams/day of HMB.11

THE ROLE OF CIRCADIAN RHYTHMS IN SARCOPENIA

Recent evidence suggests that circadian timing plays a role in triggering
skeletal muscle growth and maintaining body homeostasis. Generally, circadian rhythms are regulated by light-dark cycles, but physical activity also modulates these rhythms. Thus, preserving biological rhythms is essential for preventing and delaying sarcopenia.\textsuperscript{12}

**CONCLUSION**

Chronic Obstructive Pulmonary Disease (COPD) causes systemic inflammation, affecting both respiratory and non-respiratory muscles, leading to muscle loss and sarcopenia. Sarcopenia is influenced by neurological, endocrine, and nutritional factors. It can lead to decreased quality of life, increased hospitalization rates, mortality, and financial burdens. Sarcopenia assessment should follow AWGS 2019 guidelines and include skeletal muscle mass strength, physical performance, and appendicular skeletal muscle mass.

Pulmonary rehabilitation represents an integrated multidisciplinary management program encompassing exercise, education, behavior modification, and nutritional therapy. Exercise is the primary treatment for sarcopenia, as there is no curative therapy available. Strength resistance, aerobic exercise, balance, endurance training, and flexibility training can enhance physical performance, strength, and muscle mass are the most suitable program compositions. Motivation is also crucial for adherence to exercise programs and maintaining the exercise engram. Proper nutrition, protein intake, and vitamin D supplementation may also be beneficial.

**REFERENCES**

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