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Review Article

Sarcopenia Associated with Chronic Obstructive Pulmonary Disease

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Sarcopenia is frequently associated with chronic diseases such as chronic obstructive pulmonary disease (COPD) and cancer. COPD, which is characterized by an irreversible airflow limitation, exacerbates respiratory distress as the disease progresses. The prevalence of sarcopenia in stable COPD was reported to be 15% to 25% in previous foreign studies and 25% in a Korean study. As the amount of activity decreases, muscle mass decreases and eventually oxygen cannot be used effectively, resulting in a vicious cycle of deterioration of exercise capacity. Deconditioning due to decreased activity is a major cause of limb muscle dysfunction in patients with COPD. In these patients, the factors that decrease muscle strength and endurance include chronic inflammation, oxidative stress, inactivity, hypoxemia, hormone abnormality, deficits of nutrients such as protein and vitamin D, and the use of systemic corticosteroid. Therefore, treatment and management should either inhibit this process or should be directed toward supplementing the deficiency, such as with exercise, nutritional support, and medications and supplements. The relationship between sarcopenia and COPD is increasingly being reported, with some overlap in clinical features and treatments. We are fascinated to be able to diagnose 2 diseases through similar physical performance tests and to improve both diseases using the same treatment such as exercise. Therefore, this review summarizes the clinical relevance and integrative management of the 2 diseases.

Key Words: Chronic obstructive · Exercise therapy · Pulmonary disease · Rehabilitation · Sarcopenia · Vitamin D

INTRODUCTION

Societies are aging all over the world, and medical attention has focused on changes in body composition during the aging process. As aging progresses, lean body mass decreases and fat percentage increases.[1] These changes in metabolism cause the loss of muscle mass and lower functional status. In 1989, Rosenberg [2] first expressed medical interest in the changes in muscles that accompany aging and suggested the use of the term "sarcopenia" for aging-associated loss of muscle. Since then, sarcopenia has become a more comprehensive term that includes the concept of loss of muscle function as well as the amount of muscle. [3] If there is difficulty in moving, a gradual decline in health status, or a recent history of falls, an unintended weight loss of 5% or more may suggest sarcopenia.

[4] Sarcopenia is frequently associated with chronic diseases such as type 2 diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, rheumatoid arthritis, and cancer. The cut-off value for muscle mass is slightly different depending on the working group, and the prevalence of sarcopenia (low muscle mass) in South Korea is reported to be quite different depending on which value is used. Although systematic domestic data are still lacking, 9.3% of elderly men and 0.2% to 22.1% of elderly women are considered to have sarcopenia using the appendicular skeletal muscle mass (ASM)/height^2 (ht^2) index in the data from the Korean National Health and Nutrition Examination Survey (KNHANES).[5,6] According to the KNHANES, 13.4% of the population aged 40 years or older has COPD.[7] A relationship between sarcopenia and COPD is increasingly reported, and there is some overlap in clinical features and treatments. It is fascinating to be able to diagnose 2 diseases through similar physical performance tests and to improve both diseases through the same treatment, such as exercise. Therefore, this review summarizes the clinical relevance and integrative management of the 2 diseases.

DIAGNOSIS OF SARCOPENIA

Many diagnostic methods have been proposed at various conferences, but recently more detailed diagnostic criteria have been suggested. The European Working Group on Sarcopenia in Older People (EWGSOP) presented a European consensus on the definition and diagnosis of sarcopenia in 2010, which was updated in 2018 by EWGSOP2. EWGSOP2 used low muscle mass and muscle function (muscle strength and physical performance) as criteria for diagnosing sarcopenia. In EWGSOP2, low muscle strength is defined as the first parameter of sarcopenia, and diagnosis is confirmed by the presence of decreased muscle mass (quantity and quality). Physical performance was previously a core parameter for diagnosis, but it is now proposed as a parameter to categorize the severity of sarcopenia in the revised definition (Table 1).[1,8]

In EWGSOP2, it was confirmed that the previous cut-off values for muscle mass are difficult to memorize. For this reason, the working group decided to sacrifice precision and use cutoff points that are close to references to make them easy to remember. The Asian Working Group for Sarcopenia (AWGS) is similar to the EWGSOP, but its criteria provide other clinical guidelines. For Asian people, SMI is 7.0 kg/m^2 for men and 5.4 kg/m^2 for women when using dual energy X-ray absorptiometry (DXA), and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women when using bioimpedence analysis (BIA). In principle, the AWGS follows the diagnostic approach of the EWGSOP and revises and adds cut points in some areas from the Asian perspective. The sarcopenia project of the Foundation for the National Institutes of Health (FNIH) is designed to determine muscle strength levels associated with mobility disability and then determine the

Table 1. Operational definition of sarcopenia by European Working Group on Sarcopenia in Older People 2

	Muscle strength	Muscle quantity/quality	Physical performance
Probable sarcopenia	↓		
Sarcopenia	↓	↓	
Severe sarcopenia	↓	↓	↓

Table 2. Cut-off values for sarcopenia by EWGSOP2, AWGS, and FNIH sarcopenia project

	Muscle mass	Muscle strength	Physical performance
EWGSOP2	ASM/ht$^{2a)}$ <7.0 kg/m^2 in men <6.0 kg/m^2 in women	Grip strength <27 kg in men <16 kg in women	SPPB ≤8 Gait speed ≤0.8 m/sec TUG ≥20 sec 400 m walk test ≥6 min for completion or non-completion
AWGS	DXA$^{b)}$, ASM/ht^2 ≤7.0 kg/m^2 in men ≤5.4 kg/m^2 in women BIA$^{b)}$, SMI/ht^2 ≤7.0 kg/m^2 in men ≤5.7 kg/m^2 in women	Grip strength <26 kg in men <18 kg in women	Gait speed <0.8 m/sec
FNIH sarcopenia project	ASM/BMI <0.789 in men <0.512 in women	Grip strength <26 kg in men <16 kg in women	Gait speed <0.8 m/sec

[a]DXA is advised in clinical practice, and DXA, BIA, computed tomography or magnetic resonance imaging in research studies. [b]Defined as -2 standard deviations less than the mean of that of healthy young adults of the same sex and ethnic background.
EWGSOP2, European Working Group on Sarcopenia in Older People 2; AWGS, Asian Working Group for Sarcopenia; FNIH, Foundation for the National Institutes of Health; ASM, appendicular skeletal muscle mass; Ht, height; DXA, dual energy X-ray absorptiometry; BIA, bioimpedence analysis; SMI, skeletal muscle mass index; BMI, body mass index; SPPB, short physical performance battery; TUG, Timed Up & Go.

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level of muscle mass that would identify clinically appropriate muscle weakness. Therefore, the FNIH sarcopenia project recommends the ASM/body mass index (BMI) ratio, which is an indicator of muscle mass, divided by the BMI of ASM.[9] The cutoff values established by the international working groups are summarized in Table 2.

CLINICAL SIGNIFICANCE OF SARCOPENIA

Sarcopenia is associated with loss of mobility, falls, osteoporosis, poor quality of life (QOL) due to fracture, hospitalization, and death.[10] In addition, the loss of muscle mass and function lead to decreases in physical activity and energy consumption, resulting in an increase in body weight.[11] As a result, pulmonary function is reduced, and cardiovascular and metabolic diseases are more likely to occur. A study of the elderly in their 70s to 90s revealed that mortality increased by 1.9 times for every 1 kg/m^2 reduction of lean body mass for 2 years.[12] In Korean studies, 500 elderly patients over 65 years of age were followed up for 6 years. The mortality rate for those with sarcopenia was 2.99 times higher in men and 3.22 times higher in women than that of the normal group, based on the EWGSOP criteria.[13]

CLINICAL FEATURES OF COPD

COPD is now the fourth leading cause of death worldwide. In 2012, more than 3 million people worldwide died of COPD, accounting for 6% of all deaths.[14] COPD is an important disease in public health because it can be prevented and treated. Forced expiratory volume in one second (FEV_1), which can be confirmed by pulmonary function tests, is important for the evaluation of COPD patients. Worsening dyspnea reduces the patient's physical performance. As a result, life satisfaction is lowered and anxiety and depression may occur.[15] COPD characterized by irreversible airflow limitation exacerbates respiratory distress as the disease progresses. As the amount of activity decreases, muscle mass decreases and eventually oxygen cannot be used effectively, resulting in a vicious cycle of deterioration of exercise capacity (Fig. 1).[16] In the BODE index (BMI, FEV_1, dyspnea measured by the modified Medical Research Council, 6-min walk distance) designed for COPD mortality prediction, exercise capacity and muscle mass

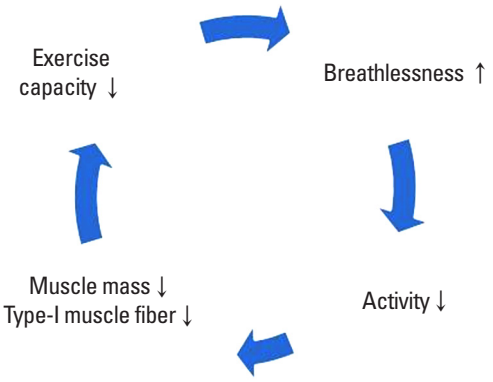

Fig. 1. Vicious cycle of inactivity in chronic obstructive pulmonary disease.

are the main prognostic factors.[17] In other words, the clinical significance of physical activity in COPD is as important as that of medical treatment.

MUSCLE DYSFUNCTION IN COPD

Deconditioning due to decreased activity is a major cause of limb muscle dysfunction. In chronic diseases such as COPD, however, problems such as inflammation, oxidative stress, malnutrition, and hypoxemia may also cause skeletal muscle dysfunction.[18] The rate of malnutrition in patients with COPD increases with the severity of the disease, up to 30% in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 4.[19] In addition, changes in body composition are reported in up to 35% of cases in which the fat free mass (FFM) index (FFMI) is significantly lower than normal.[20] Even if the BMI is normal, the evaluation of body composition is important because the FFMI is often low. One study revealed that low FFMI correlates strongly with mortality in COPD patients with normal weight.[21] In patients with COPD, atrophy of the legs, especially the thigh muscles, was dominant over the whole body.[22] In severe COPD, it was confirmed that muscle fiber shifted from type I to type IIx, unlike in the normal aging process.[23] These abnormal fiber shifts led to inefficiencies that result in high oxygen demand at submaximal workloads.[24] Systemic oxidative stress was found to be associated with endurance of the quadriceps muscle in patients with severe COPD.[25] More oxidative stress in the limb muscles and poor function of the quadriceps muscle were reported in patients with hypoxemia.[26] Quadriceps muscle strength was reported to be 20% to 30% lower in patients with COPD

than in normal people.[27] Decreased muscle endurance of the quadriceps in patients with COPD has been reported.[25,26,28] Muscle endurance was also significantly reduced with hypoxemia as well as muscle strength.[26] Many COPD patients complain of leg muscle fatigue before dyspnea, and exercise is stopped. Various studies have been conducted using subjective or objective methods. Objective methods include measuring muscle twitch after magnetic stimulation,[29] or measuring the median frequency of surface electromyography.[30] Systemic inflammation in patients with COPD has recently been identified as a cause of other complications such as cachexia and osteoporosis.[31-33] Among them, chronic inflammation in stable COPD patients is suspected as the cause of sarcopenia, and several studies are underway. Byun et al.[32] reported that high levels of high-sensitivity tumor necrosis factor-α (hsTNF-α), an inflammatory biomarker, were significant predictors of the presence of sarcopenia (odds ratio, 1.99; 95% confidence interval, 1.04–3.81) in 80 stable COPD patients.

Acute exacerbation of COPD is a condition best avoided during the course of the disease, but it is common. If acute exacerbation occurs at any time and the patient is admitted to the hospital, deterioration of systemic function including limb muscle strength can easily occur. Quadriceps muscle weakness after acute exacerbation of COPD is frequently reported, and weakened muscles recover 3 months or more after discharge.[33] Limb muscle dysfunction during acute exacerbations may be due to various factors such as systemic inflammation, malnutrition, and steroid use, as well as physical inactivity. A decreased mid-thigh muscle cross-sectional area and decreased quadriceps muscle strength contribute to increased mortality in COPD.[34] In addition, mortality was almost doubled when FFMI was less than 16 kg/m^2 in men and less than 15 kg/m^2 in women.[21] In conclusion, muscle strength, endurance, and muscle mass of the thigh are clinically important in COPD patients. For diagnosis of sarcopenia, muscle strength is measured by grip strength, not knee extensor strength, as a consensus made to simplify the diagnosis. In other words, evaluation of limb muscle dysfunction in COPD is not completely consistent with the diagnosis of sarcopenia, but it can be expected that there will be high correlation between the 2 diseases.

PREVALENCE OF SARCOPENIA IN COPD

The prevalence of sarcopenia in stable COPD was reported to be 15% to 25% in previous foreign studies and 25% in a Korean study.[32,35,36] Sarcopenia prevalence was inversely related to the modified Medical Research Council Dyspnea Scale and BODE index scores, and a higher prevalence was observed with lower 6-min walking distance.[32] The prevalence of sarcopenia in COPD patients is higher than that in normal elderly people. Therefore, COPD may be one cause of sarcopenia.[37] Physical frailty is defined as "a medical syndrome that increases the vulnerability of an individual to dependence and death due to a reduction in physical strength, endurance, and physiological function due to various causes." The frailty prevalence rate in stable COPD diagnosed with the fatigue, resistance, ambulation, illnesses, and loss of weight scale was 6.6%, 50% of which was diagnosed as sarcopenia. The prevalence of sarcopenia in the non-frail COPD group was 22.2%.[38] Frailty, sarcopenia and COPD tend to overlap some in some of their features and disease course.

MANAGEMENT OF SARCOPENIA IN COPD

In patients with COPD, the factors that decrease muscle strength and endurance include chronic inflammation, oxidative stress, inactivity, hypoxemia, hormone abnormality, deficits of nutrients including protein and vitamin D, and the use of systemic corticosteroid. Therefore, treatment and management should either inhibit this process or go in the direction of supplementing the deficient elements. Some approaches are summarized below.

1. Exercise

Pulmonary rehabilitation (PR) in patients with COPD has already been proven beneficial with high-quality evidence.[39] In other words, PR improves the exercise capacity of the patient and improves dyspnea and QOL. PR is a multidisciplinary integrated treatment program that includes exercise, education, behavior change, and nutritional therapy. Exercise refers to a planned and repetitive activity for a specific purpose over a certain period of time, with a definition different from that of physical activity. Exercise is also one of the most effective ways to improve sarcopenia. The EWGSOP noted that exercise with a primary goal of im-

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proving physical performance, strength, and muscle mass is needed for sarcopenia treatment.[1]

Exercise in sarcopenia is largely composed of resistance exercise, aerobic exercise, and balance and flexibility exercises. Intensive resistance training by elderly patients effectively increases muscle function and mass.[40] However, the elderly should perform gradual overload exercise at the intensity that they can perform. Prevention of musculoskeletal injuries is also important, and the primary purpose of exercise in sarcopenia is to improve muscle function and strength. 1 repetition maximum (RM; maximum weight that can be lifted at one time, for example, 3 RM can be repeated 3 times, but that weight cannot be lifted 4 times) is recommended, but it is somewhat burdensome for the elderly.[41] We recommend a weight repetition method that regards the weight that can be lifted 2 to 3 times as 80% of 1 RM. Generally, it is appropriate to start with 50% to 60% of 1 RM and to repeat it 12 to 15 times without causing too much muscle fatigue. If muscle strength is improved, then 1 RM should be reevaluated to gradually increase exercise intensity and gradually increase the frequency to 1 to 3 sets a day. It has been confirmed that gradual resistance exercise restores the muscle strength of the thigh muscles in frail elderly people.[42] Although it has been shown previously that the proximal thigh of COPD patients does not necessarily have a linear correlation with sarcopenia, the function of the thigh muscle plays an important role in daily activities such as walking or sitting. It is predictable that weakness of the thigh muscle eventually causes physical inactivity.

Balance exercise should be performed in the elderly, as a decreased sense of balance will make inactivity worse, and even simple aerobic exercise such as walking will be difficult to perform. A systematic review suggests that resistance exercise alone has limitations in improving postural control,[43] and balance exercise must be included to improve postural control.[44]

VO_{2max}, the maximum amount of oxygen that can be consumed during exercise, is the most useful indicator of cardiovascular endurance. In the elderly, it starts at 40% to 50% of VO_{2max} and gradually increases to 60% to 70%. In COPD patients or elderly people with sarcopenia, however, it is not easy to perform a proper exercise test. In this case, exercise intensity can be determined using the 6 min walk test (6MWT), rating of perceived exertion (RPE), and heart rate.[45] For example, an average speed of 3.0 km/hr can be calculated when walking 300 m for 6 min, and a speed of 1.8 km/hr can be determined if 60% exercise intensity is prescribed. The modified 0 to 10 Borg scale [46] is commonly used as a subjective evaluation method, and RPE is classified as 0 (inactivity) to 10 (maximal dyspnea), with recommended intensity of 3 to 5 (Table 3). Alternatively, the maximum heart rate method can be used to simply multiply the desired exercise intensity by subtracting the age of the patient from 220, which is effective when using a fitness tracker that can monitor HR in a home exercise program. Aerobic exercise should be performed at least 3 times a week and is recommended for 20 to 60 min. Most studies have shown that at least 6 to 8 weeks of treatment should be effective in improving COPD symptoms and improving cardiovascular endurance.[47] Although the most accurate aerobic exercise regimen can be prescribed with a treadmill, the recumbent cycle is often used because of the high risk of falling when the sense of balance is decreased in the elderly. However, since the cycle uses many leg muscles, aerobic exercise may not reach the appropriate intensity. Therefore, it is important to choose the exercise method according to the situation.

Table 3. Modified Borg Scale

Scale	Symptom
0	No breathlessness at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximal)
10	Maximal

Although COPD PR and exercise therapy in sarcopenia can be considered to overlap in many ways (Fig. 2), there are some additional considerations in patients with COPD. First, respiratory function is lowered compared to elderly people with sarcopenia. In particular, attention should be paid to the possibility of exercise-induced desaturation (EID) in patients with severe and very severe COPD with FEV_1 below 50%.[48] Uncorrected SpO_2 below 90% is an

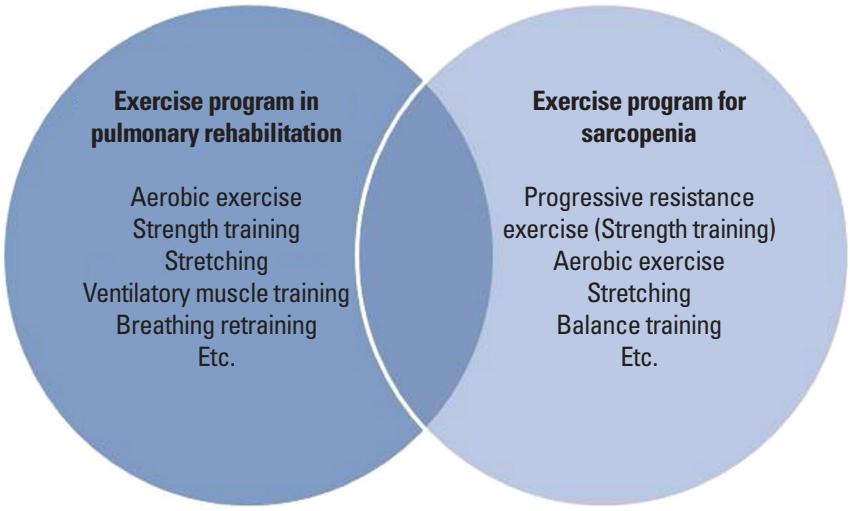

Fig. 2. Exercise program for chronic obstructive pulmonary disease and sarcopenia.

indication to terminate aerobic exercise, so if EID is identified, adequate oxygenation should be performed during exercise. Also, aerobic exercise by the elderly in the domestic environment is likely to be performed mainly outdoors. Recently, air pollution has become an issue, and fine particles can acutely exacerbate lung disease in some patients.[49] Depending on the concentration of fine particles, elderly people with lung disease may need to be told to exercise indoors.

2. Nutritional support

Malnutrition not only increases the risk of weight loss and disease but also affects sarcopenia. Protein is only used as an energy source if it is supplied with insufficient caloric intake. Therefore, sufficient nutritional supply and additional protein supply should be combined. According to the KNHANES (2014), 45.4% of elderly people under 75 years of age and 65.9% of elderly people over 75 years of age have protein intakes below recommended levels.[50] In most previous epidemiological studies, protein intake and muscle mass were positively correlated. In the Health ABC study, 2,066 elderly people were classified according to their protein intake, with less muscle loss in the 1.2 g/kg group than in the 0.8 g/kg group.[51] In some clinical trials, it has been reported that FFM increases and leg strength improves when various types of amino acids are supplied during exercise training.[52-54] However, the effect of protein alone was limited.[55] The PROT-AGE study group recommended a protein supply of 1.0 to 1.2 g/kg for healthy elderly people and 1.2 to 1.5 g/kg for elderly people with chronic or acute disease.[56] The amino acid leucine plays an important role in the process of protein catabolism. Whey protein is recommended because it has the highest leucine content. Studies comparing animal and plant proteins have also reported a positive correlation with muscle mass and animal protein intake alone.[51] An adequate protein intake for protein synthesis is 30 g or more of animal protein per serving.

Malnutrition may be common when the severity of COPD is high. Significant improvements in mid-arm muscle circumference, FFMI, 6MWT, respiratory muscle strength, and overall health-related QOL have been reported with nutritional supplementation in malnourished patients with COPD.[55] In summary, patients with COPD and sarcopenia should first be checked for malnutrition, provided adequate nutritional support, and supplied with additional forms of protein.

3. Medications

Some medicines and supplements currently available in clinical practice may be useful for patients with sarcopenia and COPD. Vitamin D is thought to play an important role in muscle metabolism, and it was recently reported that vitamin D plays a role in skeletal muscle mass and muscle strength. When vitamin D was deficient, atrophy of type II muscle fiber was confirmed.[57] Type II muscle fiber is involved in preventing falls by fast-twitching, so vitamin D supplementation can eventually lead to a reduction in fall

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risk. It was also reported that muscle performance was improved when the 25-hydroxy-vitamin D concentration was more than 60 nmol/L.[58]

Beta-hydroxy-β-methylbutyrate (HMB) is a metabolite of leucine and is often used as a nutritional supplement during muscle training. HMB increases protein synthesis through protective and anti-catabolic effects. It also stabilizes muscle cell membranes and weakens proteolytic pathways. This process can contribute to a reduction of sarcopenia. Several studies have reported the effects of HMB in reducing myalgia, lowering blood markers of musculoskeletal dissemination, increasing FFM, and improving various physical performance indicators.[59] Wu et al.[60] reported that HMB supplementation was effective in maintaining muscle mass in the elderly through a meta-analysis of seven randomized controlled trials of healthy elderly people or cancer patients aged 65 years or older. In addition, in chronic diseases including COPD, HMB was effective in preventing muscle loss, and it was reported that the usual dose of 3 g/day HMB was effective with no definite side effects.[61]

Sarcopenia is accompanied by a decreased sensitivity to insulin and steroid hormones with aging, and various studies based on the development of such hormone analogues are under way. Selective Androgen Receptor Modulator has recently been shown to be effective in the prevention and treatment of muscle wasting in clinical trials in cancer patients,[62] and clinical trials are underway for other diseases such as COPD. In addition, metformin, a diabetes drug, is undergoing further studies at the animal testing level to confirm a muscle strengthening effect.[63]

CONCLUSIONS

The market is expected to expand rapidly, as a disease code (the International Classification of Diseases, Tenth Revision, Clinical Modification code, M62.84) for sarcopenia was granted in the United States in October 2016. As a result, further research on an international scale will be conducted. Already, the European Union's innovative medicine initiative has selected the development of drugs for sarcopenia as a major health topic. In other words, sarcopenia can be expected to have a status equivalent to that of the current osteoporosis market. The diagnosis and treatment of COPD is already systematized. In addition to vaccination and smoking cessation for the prevention and treatment of COPD, the PR has also gradually expanded in South Korea. In conclusion, if physicians are interested in COPD PR, it is possible to evaluate, prevent, and treat sarcopenia easily. In COPD patients, sarcopenia can be diagnosed through tests such as the grip test, DXA or BIA, and gait speed. Standardization of the evaluation guideline will facilitate investigation of the prevalence of sarcopenia in domestic COPD patients and enable effective exercise to be prescribed for the treatment of patients with sarcopenia with COPD.

DECLARATIONS

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Ethics approval and consent to participate

Not applicable.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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