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REVIEW ARTICLE

Nutritional supplementation in patients with chronic obstructive pulmonary disease

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Malnutrition in patients with chronic obstructive pulmonary disease (COPD) is associated with cachexia, sarcopenia, and weight loss, and may result in poorer pulmonary function, decreased exercise capacity, and increased risk of exacerbations. Providing nutritional supplementation is an important therapeutic intervention, particularly for severely ill COPD patients with malnutrition. Higher calorie intake through nutritional supplementation significantly increases body weight and muscle strength, and improves quality of life in malnourished COPD patients. Difficulties may be experienced by these COPD patients, who are struggling to breathe and eliminate CO_2 from the lungs, resulting in dyspnea, hypercapnia, hypoxia, and respiratory acidosis, which exacerbates muscle loss through oxidative stress and inflammatory responses. To overcome these problems, nutritional supplements should aim to reduce metabolic CO_2 production, lower respiratory quotient, and improve lung function. Several studies have shown that high-fat supplements produce less CO_2 and have lower respiratory quotient value than high-carbohydrate supplements. In addition, high-fat supplements may be the most efficient means of providing a low-volume, calorie-dense supplement to COPD patients, and may be most beneficial to patients with prolonged mechanical ventilation where hypercapnia and malnutrition are most pronounced. Further studies are required to investigate the optimal nutritional supplements for COPD patients according to their disease severity.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease caused mainly by long-term exposure to cigarette smoke and other harmful airborne pollutants. Permanent damage to the lung parenchyma with loss of elastic recoil causes emphysema and inflammatory cell infiltration of the walls of the small airways, resulting in chronic bronchiolitis and bronchitis. The severity of COPD was classified according to measurements of airflow obstruction by determining the degree of FEV_1 (forced expiratory volume in the 1st second) reduction. However, FEV_1 alone does not reliably identify severity of breathlessness, exercise limitation, or impairment of health. The Global Initiative for Obstructive Lung Disease has published the classification system for COPD disease severity with revising the staging system based on FEV_1 alone.[1] This classification may allow diagnoses of 60—85% of undiagnosed patients who have mild to moderate disease.[1,2] The new Global Initiative for Obstructive Lung Disease guidelines categorize COPD patients into four groups by combining the spirometric measurements with symptomatic assessments, using established questionnaires (COPD Assessment Test, Clinical COPD Questionnaire, or modified Medical Research Council Dyspnea Scale), and the evaluation of the risk of future exacerbations, based on the patient's history of exacerbations in the previous year.[1]

There is no cure for COPD patients, and the major goals of treatments involve management of the patients' symptoms. As well as reduced lung function, patients with COPD tend to have poor health related quality of life, with approximately a third of these patients suffering from malnutrition. Their breathing difficulties not only affect their exercise capacity but also cause a loss of appetite and decreased nutritional intake, resulting in a spiraling malnourished state. Malnutrition is more common in patients with emphysema than chronic bronchitis, and may be either a cause of further degeneration of the disease or a consequence of disease progression.[3,4]

There is mounting evidence that in COPD patients with low body mass index and/or fat-free mass index (FFMI) are associated with a poorer prognosis and impaired long-term survival.[3] Malnutrition further aggravates the problems in COPD patients as respiratory muscle strength is reduced leading to cachexia, with a significant loss of appetite and exercise intolerance.[5—7] Furthermore, COPD patients tend to be elderly, and the loss in skeletal muscle mass as part of the natural aging process, may be further exacerbated by COPD as a result of malnutrition, sarcopenia, and cachexia.[6]

Sarcopenia is defined as the loss of skeletal muscle mass through the inability to generate new muscle cells, and also through the atrophy of existing muscle fibers.[6,8] The relationship among sarcopenia, physical performance, and respiratory function test was investigated in 71 patients with COPD aged $>$ 65 years.[9] In these well-nourished COPD patients, linear regression analysis revealed that respiratory function was a better predictor of physical performance compared with body muscle mass parameters. However, in sarcopenic COPD patients with moderate disease severity, the proportion of fat-free mass (FFM) was significantly reduced compared with healthy matched controls, although the fat mass was similar between the two groups, suggesting a similar lipolytic rate.[10]

It is widely accepted that COPD patients who are malnourished with low body weight are at greatest risk of further exacerbations,[11] with increased risk of hospital readmittance,[12] and have higher mortality rates.[13] Interestingly, in COPD patients who were considered to be overweight or obese, there was evidence of a reduced risk of hospitalization, and reduced mortality rates.[11—13] The reason that these overweight/obese patients have a better prognosis is probably attributable to the physiological advantages.

There is mounting evidence from large, multicenter studies demonstrating that in patients with moderate to severe COPD, low FFMI was a statistically significant predictor of mortality, independent of other factors.[14—17] In the elderly COPD population, sarcopenia is accelerated by as much as 30% in patients with mild to moderate COPD.[16] This is in addition to skeletal muscle loss due to the natural process of aging. The results from these studies support the assessment of body composition as a very important diagnostic marker of disease severity in COPD.

Inflammation in COPD

There is evidence to suggest that, in addition to inflammatory responses to the respiratory tissues, inflammation may be an important factor affecting the loss of skeletal muscle mass in COPD patients. The detection of high levels of circulating proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1β in COPD patients with cachexia, have led to claims that COPD is a "chronic systemic inflammatory syndrome."[18] Systemic inflammation and oxidative stress do play a role as pathological mechanisms involved in muscle dysfunction in COPD.

Chronic inflammation may have a detrimental effect on muscle catabolism. The action of inflammatory cytokine TNF binding to its receptor on muscle cells results in apoptotic muscle cell death. Furthermore, muscle anabolism may be affected during chronic inflammation as the available amino acid pool may become depleted, through synthesis of acute phase proteins, thus preventing replenishment of muscle protein stores.[19] Indeed, glutamate, the amino acid salt form of glutamic acid, has been shown to be low in concentration in the plasma of COPD patients.[19] Cachectic COPD patients with moderate disease have lower plasma concentrations of glutamate and branched-chain amino acids (BCAAs) than those in the control and noncachectic COPD groups, and demonstrate a higher whole-body myofibrillar protein breakdown.[19]

Oxidative stress in COPD

In addition to chronic inflammation, oxidative stress may further aggravate muscle degeneration and other symptoms in COPD patients. There may be an imbalance between O_2 and CO_2 levels in the blood, creating hypoxic conditions in the cells and muscles, leading to the production of reactive oxygen species. It has been proposed that the loss of muscle mass in COPD patients may not solely result from physical inactivity, but that hypoxia, oxidative stress, and muscle dysfunction also play a significant role.[20] The