Nutritional targets to enhance exercise performance in chronic obstructive pulmonary disease

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Purpose of review
This review presents current knowledge regarding the rationale and efficacy of nutrition as an ergogenic aid to enhance the effects of exercise and training in chronic obstructive pulmonary disease (COPD).

Recent findings
Altered body composition and skeletal muscle dysfunction in COPD suggest that exercise capacity can be targeted via several metabolic routes. Muscle metabolic alterations in COPD include a reduced oxidative metabolism and enhanced susceptibility for oxidative stress. Muscle wasting may be associated with deficiencies of vitamin D and low branched-chain amino acid levels. Exercise training is of established benefit in COPD but clear-cut clinical trial evidence to support the performance enhancing effect of nutritional intervention is lacking. One randomized controlled trial suggested that augmentation of training with polyunsaturated fatty acids may improve exercise capacity. Conflicting results are reported on dietary creatine supplementation in patients with COPD receiving pulmonary rehabilitation and results from acute intervention studies do not directly imply long-term effects of glutamate or glutamine supplementation as an ergogenic aid in COPD. Recent data indicate that not only muscle but also visceral fat may be an important additional target for combined nutrition and exercise intervention in COPD to improve physical performance and decrease cardiometabolic risk.

Summary
There is a clear need for adequately powered and controlled intervention and maintenance trials to establish the role of nutritional supplementation in the enhancement of exercise performance and training and the wider management of the systemic features of the disease.

Keywords
chronic obstructive pulmonary disease, exercise, nutrition, pulmonary rehabilitation, skeletal muscle

INTRODUCTION

Although lung damage is the initiating event in chronic obstructive pulmonary disease (COPD), the severity of lung function impairment relates poorly to physical incapacity and symptoms. Disability in COPD is now recognized as the consequence of a complex chain of events centering around the 'disability spiral' (Fig. 1) in which exercise-related breathlessness results in activity avoidance, deconditioning and worsening exercise intolerance. The pathophysiological consequence is impaired skeletal muscle function (particularly in the locomotor muscles) and there is now compelling evidence that this is a key determinant of exercise intolerance and activity limitation in COPD. This is important because skeletal muscle impairment is a potentially treatable feature of a disease in which the primary pulmonary pathophysiology is largely irreversible. Pulmonary rehabilitation with exercise training as core intervention is effective in improving exercise performance in COPD and provides proof of concept that this approach is profitable

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KEY POINTS

- Nutritional strategies can be considered as ergogenic aids to enhance efficacy of pulmonary rehabilitation, but may also target specific muscle disease in COPD including muscle wasting and altered regulation of muscle oxidative metabolism.

- Adequately powered intervention and maintenance trials are needed to establish the role of nutritional supplementation in the enhancement of exercise performance and training and the wider management of the systemic features of COPD.

[1]. However, there is considerable interest in other nutritional or anabolic therapies that might improve exercise capacity either by augmenting the physical training component of pulmonary rehabilitation or delivering benefits to patients who are unable to access pulmonary rehabilitation or have other barriers (e.g. musculoskeletal conditions) to perform whole body exercise training. Apart from increased resting energy expenditure, activity-induced energy expenditure is increased, which is an important contributor to elevated total daily energy expenditure [2] and may be explained by a decreased mechanical efficiency, the chemical conversion of energy to mechanical work, during lower limb exercise [3]. In line, higher ATP costs of muscle contraction in COPD patients versus controls were recently reported [4]. Consequently, exercise training is not only a stimulus for skeletal muscle but may also increase energy requirements that can induce weight loss in susceptible patients.

Nutritional strategies, therefore, can be considered as ergogenic aids to enhance efficacy of pulmonary rehabilitation but may also target specific muscle disorder in COPD including muscle wasting and altered regulation of muscle oxidative metabolism.

In this review we will primarily consider the use of nutrition as an ergogenic aid to enhance the effects of exercise and training. It should be born in mind, however, that nutritional depletion itself is an important clinical manifestation of COPD, and therefore maintaining or improving nutritional status is an important therapeutic goal in this population. It is generally considered important to enhance nutritional therapy with an anabolic stimulus such as exercise, which is the converse of the approach we will consider in this article, and has different objectives (improvement in BMI and lean mass as opposed to exercise performance). Although both objectives may be considered clinically important, the target patient population and outcome measures will differ depending on the overall aims of the intervention.

ALTERED BODY COMPOSITION AND SKELETAL MUSCLE DISORDER

Skeletal muscle dysfunction is characterized by loss of muscle mass, strength and endurance together with intrinsic abnormalities in peripheral skeletal muscle morphology and metabolism. Muscle
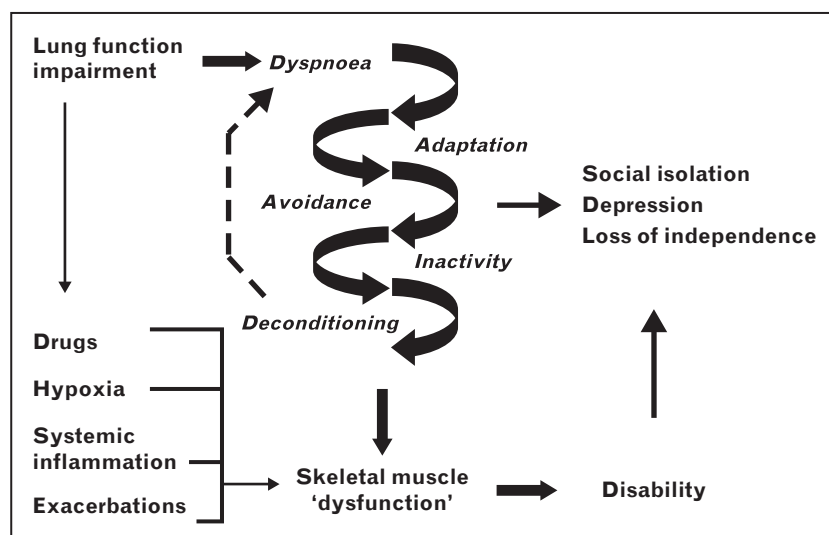

FIGURE 1. The disability spiral in COPD. This figure illustrates the multifactorial nature of disability in COPD. In this model, lung damage leads to exercise induced dyspnoea, adaptation of lifestyle to avoid physical activity and subsequent loss of fitness and further dyspnea, the so-called 'spiral of disability'. The consequence of this process is impaired skeletal muscle function, which may also be influenced by other disease features.

wasting is not only confined to weight-losing patients but also seen in weight-stable COPD patients [5]. Recent studies have suggested that although fat mass may be preserved relative to muscle mass, fat is redistributed to the visceral compartment [6,7,8""]. Increased visceral fat results in a higher cardiometabolic risk, which may also be heightened by decreased insulin sensitivity in normal-weight patients and be an important additional target of exercise training [9",10].

Structural and functional abnormalities in the skeletal muscles of patients with COPD include reductions in the proportion of type I fibers [11], mitochondrial oxidative enzyme concentrations [12] and mitochondrial density [13]. The functional consequence is excessive glycolytic and reduced oxidative metabolism during exercise, which is associated with early lactate rise and adenine nucleotide loss, even at the low absolute exercise intensities that patients with COPD can achieve [14].

The cause of skeletal muscle dysfunction in COPD is probably multifactorial, involving the interaction of lifestyle changes (reduced habitual physical activity, smoking [15,16]) with disease-specific factors (e.g. hypoxia, systemic inflammation, oxidative stress and drug therapy such as β agonists or corticosteroids). Nutritional factors may also be implicated as calorie intake, which may be reduced in some patients due to poor appetite, respiratory discomfort during meals due to hyperinflation and socioeconomic factors impairing the quality of the diet. Generally, reduced calorie intake in relation to expenditure leads to alterations in the fat compartment rather than the lean compartment and can more easily be overcome by calorie supplementation.

Skeletal muscle dysfunction in patients with COPD can be at least partially reversed by physical training [17,18]. Training adaptations are generally mode specific with improvements in muscle strength and mass seen following resistance training and muscle oxidative capacity improvement following aerobic training. Controversy remains about whether skeletal muscle function can be returned to the healthy state by physical training. In practice this is difficult to ascertain given the wide range of normal muscle physiology in healthy older people. Moreover, practical barriers to the delivery of sustained, high intensity exercise training in patients with a chronic disease such as COPD mean that the potential to enhance physical training with adjunctive nutritional interventions remains. This is further supported by the practice of elite athletes in paying careful attention to nutritional intake during training and competition. A caveat to the

translation of this technology to the field of COPD are the generally small increments in performance athletes aim to achieve which in all likelihood would be insufficient to deliver meaningful benefits in a clinical rehabilitation setting. In the remainder of this review we will consider specific macronutritional and micronutritional interventions that have been tested in COPD.

SCIENTIFIC EVIDENCE FOR NUTRITIONAL INTERVENTIONS

Both macronutrients and micronutrients are of interest as ergogenic aids to enhance the effects of exercise and training in COPD.

Carbohydrate supplementation

Early concerns about adverse effects of carbohydrate (CHO) supplementation in COPD, due to increased CO_2 production resulting from CHO oxidation loading ventilation, have not been substantiated in more recent studies [19]. Moreover, from the perspective of enhancing physical performance, there is a strong rationale for prioritizing CHO intake during exercise training in COPD. Deconditioned patients may be unable to utilize fat as an energy substrate and are, thus, highly reliant on CHO. This is likely to apply to generally inactive and deconditioned COPD patients with a decreased fat oxidative metabolism [20]. Moreover, oral nutritional supplements with a higher CHO and lower fat composition may be beneficial, as digestible CHOs are a rapid energy source in the muscle. They empty rapidly from the stomach, thereby limiting satiety that will reduce normal food intake. This is especially relevant for COPD patients who experience poor appetite because of postprandial shortness of breath, as CHO-rich supplements induce less shortness of breath than fat-rich supplements [19].

Steiner *et al.* [21] investigated the impact of CHO-rich supplementation during outpatient pulmonary rehabilitation versus placebo. Improvements in body weight were seen in the supplemented group, but principally in the fat compartment. Patients allocated to placebo lost weight during rehabilitation, suggesting significant energy cost of the program, which could be overcome with supplementation. No improvement in muscle mass was seen, but this might have been due to the nature of the exercise program which comprised low intensity aerobic rather than resistance training. Gains in whole body exercise performance were seen only in well nourished patients and improvements in exercise capacity were correlated with the increased CHO intake. These findings suggest that CHO

supplementation may be a fruitful approach to enhance exercise training, but the observation of a positive effect in a subgroup only requires replication in further trials before recommendations can be made for clinical practice.

Protein and amino acid supplementation

Given that lean tissue wasting and muscle weakness are important systemic features of COPD, augmenting muscle protein synthesis with additional dietary protein is an attractive approach. Furthermore, enhanced levels of resting whole body protein turnover have been consistently reported in COPD [22,23▪], associated with an elevated resting metabolic rate. Dietary amino acids stimulate protein synthesis in health although this effect may be blunted in older people, a phenomenon termed 'anabolic resistance' [24]. The optimal protein feeding at the time of exercise may be an effective method for facilitating the anabolic effect of dietary supplementation in undernourished or weight-losing patients. This may also be particularly relevant in view of a suppressed whole-body protein and urea turnover after low intensity exercise in COPD patients with emphysema [25,26]. Evidence that anabolic resistance is of importance in COPD is lacking, indeed studies of amino acid feeding in COPD suggest that protein synthesis was stimulated. Despite the appearance that supplementation of dietary protein (>1.5 g/kg per day) is generally advised to increase muscle mass [27], the optimal amount of protein to stimulate net protein synthesis in wasted COPD patients is still not determined.

Apart from protein metabolism, there is an increased interest in specific amino acid metabolism in the context of loss of muscle mass. Indeed, COPD patients with muscle atrophy have been shown to have low plasma levels of branched-chain amino acids (BCAA), especially leucine, compared with age-matched controls. Additionally, plasma levels of BCAA positively correlate with fat free mass (FFM) in patients with COPD [28]. It is generally acknowledged that BCAA, in particular leucine, is able to stimulate the anabolic mammalian target of rapamycin (mTOR) signaling cascade and protein synthesis [29]. Recently, it was elegantly shown in vitro that leucine supplementation stimulates myofibrillar protein rather than generic protein accretion in skeletal muscle, and that this involves pretranslational control of myosin heavy chain (MyHC) expression of leucine in an mTOR-independent and dependent manner [30▪▪]. Glutamate is another (nonessential) amino acid known to play an important role in metabolic routes in skeletal muscle. Glutamate is a precursor for the first and rate-limiting step in glutathione (an important antioxidant in muscle) synthesis and is also involved in preserving high-energy phosphates in muscle at rest and during exercise [31,32]. Decreased muscle glutamate concentration in COPD is consistently reported and is associated with decreased muscle glutathione concentration and early lactic acidosis [33], whereas plasma glutamate concentration is positively associated with FFM [34].

Although most caloric intervention studies used protein-rich supplements [35], only a few studies specifically explored the impact of protein supplementation in COPD. Baldi et al. [36] randomized COPD patients with weight loss to receive an amino acid mixture with high BCAA concentrations (total protein intake >1.5 g/kg) embedded in a 12-week rehabilitation program or no supplementation. Body weight and FFM significantly increased in the essential amino acid supplementation group but not in the control group. These results are in line with an acute experiment in normal weight COPD patients with mild muscle wasting [37], in which BCAA supplementation to soy protein enhanced whole body protein synthesis and altered interorgan protein metabolism in favor of the peripheral (muscle) compartment. The effect was more pronounced in COPD than in healthy age-matched controls. Conversely, continuous oral glutamate ingestion for 80 min did not lead to acute effects on skeletal muscle substrate metabolism and muscle performance in COPD patients as well as in healthy age-matched controls [38]. In line with this, Marwood et al. [39▪] hypothesized that glutamine supplementation prior to exercise would enhance V(O2) peak, V(O2) at lactate threshold and speed pulmonary oxygen uptake kinetics in COPD. Patients consumed 0.125 g/kg of L-glutamine 1 h before exercise, but no improvement of oxidative metabolism were observed.

Polyunsaturated fatty acid supplementation

Research by Remels et al. [40] demonstrated reduced peroxisome proliferator-activated receptor (PPAR)-c coactivator-1α mRNA expression, PPAR δ-protein levels and mitochondrial transcription factor A content in skeletal muscle of COPD patients. As these are important regulators of mitochondrial biogenesis, skeletal muscle oxidative capacity and fiber-type shifting towards more oxidative fibres, these findings imply disturbed regulation of muscular oxidative capacity. They also produced experimental and clinical evidence for the effect of inflammation on skeletal muscle oxidative capacity in a nuclear factor (NF)-κB-dependent manner, next to known factors as inactivity and hypoxia [41].

Experimental research has shown that polyunsaturated fatty acids (PUFAs) improve muscle maintenance by modulating systemic inflammation and NF-κB [42]. PUFAs are furthermore natural ligands of PPARs and dietary intake of n-3 and n-6 fatty acids is associated with serum inflammatory markers. Specifically, higher (anti-inflammatory) n-3 fatty acid intake was related to lower serum tumor necrosis factor α (TNFα), whereas (proinflammatory) n-6 fatty acid intake was related to elevated interleukin (IL) 6 and C-reactive protein (CRP) [43].

Early nutritional supplementation studies used fat-rich supplements not for their immune modulating properties but because of concerns about adverse effects of CHO on ventilation in COPD. Sugawara *et al.* [44] investigated in a nonplacebo randomized-controlled trial (RCT) the effects of oral nutritional supplementation, enriched with PUFA, vitamins A, C and E, incorporated into a 12-week home-based pulmonary rehabilitation program in 36 elderly normal to underweight patients with COPD. Positive effects were shown on fat mass, respiratory muscle strength, 6 minute walking distance (6MWD) and systemic inflammation. A placebo-controlled RCT by Broekhuizen *et al.* [45] investigated the effect of an n-3/n-6 PUFA mixture on top of pulmonary rehabilitation. This study did not show a positive effect on the systemic inflammatory profile, which could be related to the short 8 weeks intervention duration. However, they did show a significantly enhanced improvement in endurance exercise capacity independent of muscle mass and strength, which could imply a stimulating effect on muscle fat oxidative metabolism.

Vitamin D supplementation

Recent data showed that vitamin D deficiency occurs very frequently in patients with COPD [46]. Vitamin D is involved in several COPD-related disease features, including impaired lung function [47], osteoporosis [48▪] and compromised immune function, but it is also suggested to affect muscle strength and function [49▪]. Responsible processes for cellular effects of vitamin D on muscle cells include calcium homeostasis, cell proliferation and differentiation, protection of skeletal muscle cells against insulin resistance, and arachidonic acid mobilization [49▪]. Both genomic and rapid nongenomic mechanisms mediate these processes via the vitamin D receptor [50]. In line with previous findings, a cross-sectional study by Romme *et al.* [48▪] detected vitamin D deficiency (plasma 25(OH)D concentration <50 nmol/l) in the majority of the moderate-to-very severe COPD patients, and reported a positive association of plasma 25(OH)D

concentration with bone mineral density and exercise capacity. However, a recent study by Jackson *et al.* [51] investigated whether vitamin D levels contribute to muscle dysfunction in COPD, but an association was not found. A meta-analysis in healthy adults defined a positive effect of vitamin D supplementation on muscle strength in patients with plasma 25(OH)D concentrations less than 25 nmol/l, although supplementation had no effect in patients with plasma 25(OH)D above this concentration [52].

To date, no studies have explored the impact of vitamin D supplementation on exercise performance or the outcome of exercise training in COPD. In a single center RCT, vitamin D supplementation did not reduce exacerbation frequency or improve lung function in COPD [53▪]. Measures of exercise capacity or body composition were not reported in this study. Nevertheless, well designed RCTs are needed to determine whether vitamin D supplementation benefits the treatment of exercise limitation in COPD.

Creatine supplementation

Creatine is a widely available nutritional supplement, which in its phosphorylated form enhances performance by increasing the phosphagen pool available for rapid resynthesis of ATP from adenosine diphosphate during periods of high ATP turnover.

Several studies have explored the potential enhancing effect of dietary creatine supplementation in COPD patients receiving pulmonary rehabilitation with conflicting results. In the study by Fuld *et al.* [54] creatine supplementation led to increases in FFM, peripheral muscle strength and endurance, but not exercise capacity. In contrast, two other studies [55,56] did not show an enhancing effect. These differences are probably due to dissimilarities in the studied patient characteristics and the content of the exercise training programs. In a subsequent systematic review [57] the authors conclude that creatine supplementation cannot currently be advised as an adjunct to pulmonary rehabilitation.

Antioxidant supplementation

The process of oxidative stress results from an imbalance between oxidants and antioxidant capacity and is a well known feature in COPD. Moreover, oxidative stress is linked to peripheral muscle dysfunction [58–60] and exercise intolerance [61]. Taken together, data from studies on muscle oxidative damage indicate that COPD peripheral muscle fibers are exposed to oxidative stress. The

excessive reactive oxygen species mainly target mitochondria and myofilaments, resulting in muscle apoptosis, dysfunction of mitochondrial respiratory chain, and altered contractile properties of myofilaments [59]. Pressurized whey has antioxidant and nutritional properties, which may improve exercise tolerance and enhance the effects of exercise training in patients with COPD.

Laviolette *et al.* [62] provided their COPD patients with 20 g active pressurized whey or placebo (casein) daily for a 16-week period, accompanied by an exercise training program in the last 8 weeks. Endurance time improved statistically significant, but surprisingly systemic inflammatory and oxidative stress markers were not significantly modified.

Nutritional rehabilitation as part of integrated care

It is now recognized that patients with COPD are best managed through multimodal therapies delivered through an integrated healthcare system. These interventions may include pharmacological therapies, pulmonary rehabilitation, oxygen therapy and smoking cessation. Muscle wasting is not necessarily limited to advanced disease, and therefore may be of benefit when incorporated into such integrated care programs.

An INTERdisciplinary COMmunity-based COPD management program (INTERCOM) consisting of 4 months exercise training and standardized nutritional supplements followed by a 20-month maintenance program (nutritional counseling and supplements upon indication) was also effective in COPD patients with exercise impairment but less advanced airflow obstruction [63]. Additionally, a prescheduled post-hoc analysis of muscle-wasted COPD patients participating in INTERCOM resulted in significant long-term effects on FFM, skeletal muscle function and 6MWD compared with usual care [64]. Moreover, cost-analysis revealed significantly lower hospital admission costs in the intervention group [65]. As the control group received usual care, the relative influence of exercise and nutrition could not be identified. At the other end of the disease spectrum, Pison *et al.* [66■] studied the impact of a multicomponent intervention (nutritional supplementation, exercise and testosterone therapy) in a cohort of patients with respiratory failure. Improvements in exercise performance and health status were seen in the treatment group. Tantalizingly although not statistically significant in the intention to treat analysis, the intervention improved survival when patients who completed the protocol were considered.

CONCLUSION

Nutritional strategies can be considered as ergogenic aids to enhance efficacy of pulmonary rehabilitation, but may also target specific muscle disorder in COPD including muscle wasting and altered regulation of muscle oxidative metabolism. Although the rationale for both BCAA and vitamin D supplementation seems highly promising, remarkably few studies specifically explored the impact of supplementation on exercise performance or the outcome of exercise training in COPD. There is good evidence from one RCT that PUFA on top of pulmonary rehabilitation may improve exercise capacity [45], but this should be confirmed in other trials. Conflicting results are reported on dietary creatine supplementation in patients with COPD receiving pulmonary rehabilitation and results from acute intervention studies do not directly imply long-term effects of glutamate or glutamine supplementation as ergogenic aid in COPD. Furthermore, altered visceral fat distribution is an additional target for combined nutrition and training in COPD. There is a clear need for adequately powered intervention and maintenance trials to establish the role of nutritional supplementation in the enhancement of exercise performance and training and the wider management of the systemic features of the disease.

Conflicts of interest
There are no conflicts of interest.

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