New treatments for chronic obstructive pulmonary disease using ergogenic aids*

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ABSTRACT

Chronic obstructive pulmonary disease is currently considered a systemic disease, presenting structural and metabolic alterations that can lead to skeletal muscle dysfunction. This negatively affects the performance of respiratory and peripheral muscles, functional capacity, health-related quality of life and even survival. The decision to prescribe ergogenic aids for patients with chronic obstructive pulmonary disease is based on the fact that these drugs can avert or minimize catabolism and stimulate protein synthesis, thereby reducing the loss of muscle mass and increasing exercise tolerance. This review summarizes the available data regarding the use of anabolic steroids, creatine, L-carnitine, branched-chain amino acids and growth hormones in patients with chronic obstructive pulmonary disease. The advantage of using these ergogenic aids appears to lie in increasing lean muscle mass and inducing bioenergetic modifications. Within this context, most of the data collected deals with anabolic steroids. However, to date, the clinical benefits in terms of increased exercise tolerance and muscle strength, as well as in terms of the effect on morbidity and mortality, have not been consistently demonstrated. Dietary supplementation with substances of ergogenic potential might prove to be a valid adjuvant therapy for treating patients with advanced chronic obstructive pulmonary disease, especially those presenting loss of muscle mass or peripheral muscle weakness.

Keywords: Lung diseases, obstructive; Respiratory muscles; Dietary supplements; Anabolic agents/therapeutic use; Exercise; Energy metabolism

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitation that is not fully reversible. It is typically progressive and accompanied by an abnormal inflammatory response of the lungs to noxious gases or particles.[1] Although the drug therapy is specifically designed for the primarily affected organ, the lung, the impact of the bronchodilator and anti-inflammatory therapy on exercise capacity can be modest.[2]

This fact can be explained by new evidence that indicates that skeletal muscle dysfunction syndrome, characterized by atrophy (sarcopenia) and loss of muscle strength, is an important factor for the decreased exercise tolerance seen in patients with COPD.[3] The etiology of this syndrome seems to be multifactorial, involving deconditioning, systemic hypoxia or hypercapnia, as well as alterations induced by age, drugs and nutritional depletion.

Progressive weight loss is a common finding in this disease and can be identified in up to 50% of patients, especially in those with predominant pulmonary emphysema.[4] Such weight loss is a negative prognostic factor, regardless of the degree of airway obstruction,[5] and has been correlated with increased morbidity and mortality[6] (Figure 1). An energy imbalance, caused by reduced consumption and increased basal energy metabolism, seems to be associated with weight loss.[7] Weight loss is commonly accompanied by a reduction in skeletal muscle mass,[8] probably due to systemic inflammation, which is characterized by high levels of TNF-[9] and IL-6 (potentially involved in the anorexia seen in these patients), hypoxia (contributing to low peripheral oxygen saturation with consequent negative effects on the structure and function of the skeletal muscle), dyspnea (which results in lower food intake) and physical inactivity. Finally, it is notable that malnutrition itself[10] results in protein metabolization as a way of obtaining substrate (Figure 2).[11]

In healthy individuals, ergogenic supplementation is used to increase exercise tolerance, postpone fatigue or stimulate muscle protein synthesis, thus improving physical performance.[12] In patients with COPD, the use of hormone and protein supplementation is intended to bring ergogenic benefits, especially those related to increased synthesis or decreased protein metabolism.[13]

The objective of this review was to summarize the current knowledge about the supplementation of ergogenic substances in patients with COPD, providing the theoretical bases for its rational use in the clinical context. We included articles and abstracts published between 1980 and 2005, written in English or Portuguese, indexed in the LILACS, Pubmed or Medline databases and related to the supplementation of ergogenic substances for patients with COPD. It should be specifically noted that the present review does not cover energy/caloric supplementation or the optimization of nutritional support for patients with COPD.

ANABOLIC STEROIDS

Anabolic steroids are synthetic hormones similar to testosterone, which is the most important

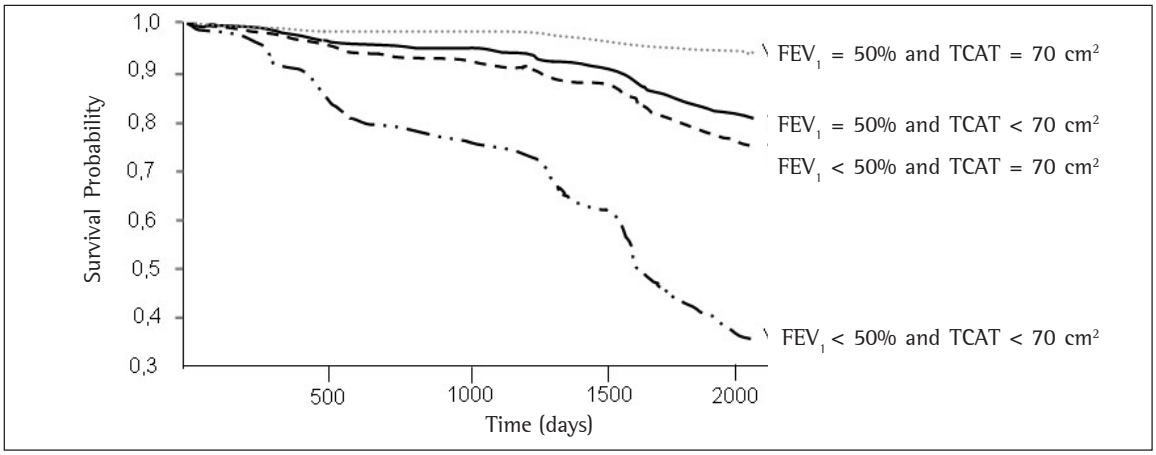

Figure 1 - Survival curve based on FEV1 and transversal cross-sectional area of the thigh (TCAT)(5)

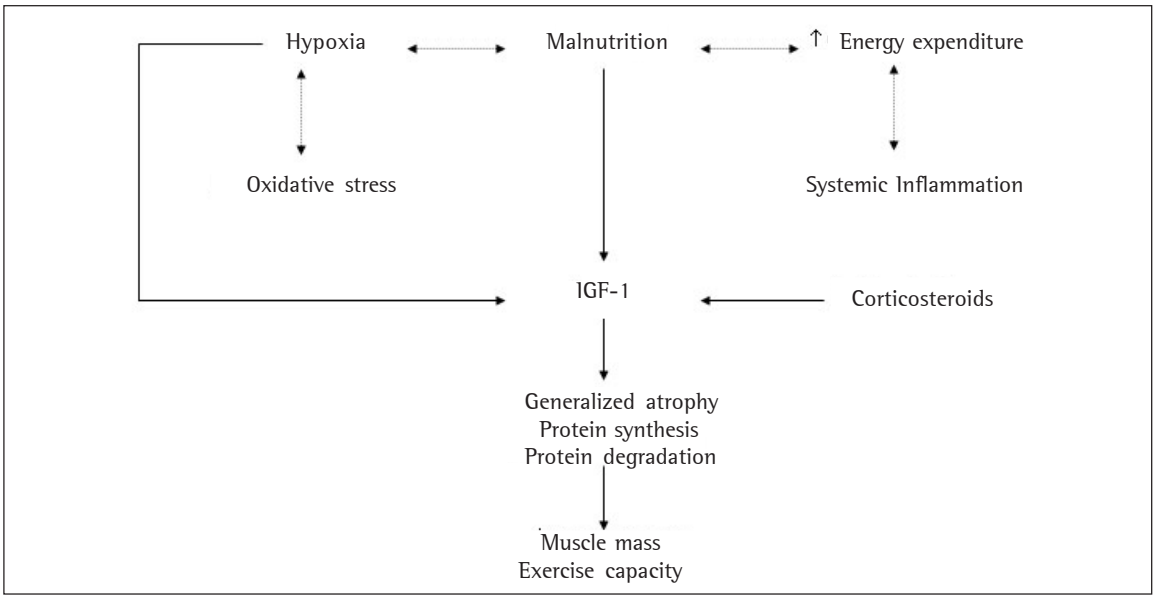

Figure 2 - Possible mechanisms negatively influencing insulin-like growth factor 1(IGF-1) and their skeletal muscle consequences

hormone secreted by the interstitial cells of the testis. They affect the development of the male sexual characteristics, promoting muscle hypertrophy and reduction of body fat.[14]

In humans, the prolonged use of high doses of anabolic steroids can result in the deterioration of the normal endocrinal function of the testosterone and increased concentration of estradiol, a female hormone that promotes the development of female characteristics. Other side effects, such as higher cholesterol (with lower levels of high density lipoprotein), liver injury, prostatic hyperplasia, impotence and sterility, can occur.[12] The significant anabolic effect of steroids has stimulated various researchers to investigate the potential therapeutic effects of these substances (Chart 1).

Intramuscular administration of nandrolone decanoate (Deca-Durabolin®) was used in a study that involved patients with moderate to severe COPD, with and without muscle depletion.[14] Different doses were used for males (50 mg) and females (25 mg) for 8 weeks. An interesting observation made by the authors was that the depleted patients who received hypercaloric supplementation (420 kcal) in addition to nandrolone presented greater weight gain, lean body mass and respiratory muscle strength than did the individuals who received only nutritional supplementation.

In a randomized, controlled clinical trial conducted in Brazil, stanozolol supplementation (12 mg per day delivered orally for 27 weeks) and intramuscular administration of testosterone (a single 250 mg dose given at baseline) was evaluated in patients with low body weight (body mass index lower than 20 kg/m2) and reduced maximal inspiratory pressure (< 60% of predicted).[15] Concomitant training of inspiratory muscles and lower limbs was administered using a cycloergometer. Those authors observed significant increases in body mass index, lean body mass, and muscle circumference of arm and thigh in the supplemented group in relation to the control group (placebo combined with training). However, no changes were observed in the 6-minute walk test results or in maximum exercise capacity.

In another study, oxandrolone supplementation (10 mg, orally, for four months) was given to patients with moderate to severe COPD presenting mean forced expiratory volume in 1 second (FEV_1) of 34 ± 15.8% of predicted and with low body weight (90% of the ideal).[16] The authors observed increased body weight, mainly in terms of lean body mass, clinically significant increases in the distance covered on the 6-minute walk test (> 65 meters for most patients) and progressive decreases in the use of medication. The most common side effect was edema (seen in 17%), which was treated by reducing

Chart 1 - Main characteristics of studies that used anabolic steroids in patients with COPD

Author, year	N at patients Controls	Inclusion criteria	Supplementation	Results
Schols et al, 1995	110/107	moderate to severe COPD	Nandrolone Decanoate ♂50mg: ♀25 mg) for 8 weeks	Weight and MIP: ↑ (depleted) Lean body Mass: ↑ (depleted or undepleted) 6MWT: =
Ferreira et al, 1998	10/7	♂ EMI < 20 kg/m² MIP < 60% predicted	Testosterone 250 mg in the basal period and stanozolol 12 mg for 27 weeks	BMI: ↑ Lean body mass: ↑ 6MWT: =
Yeh et al, 2002	55/0	moderadate to severe COPD Weight ≤ 90% ideal	Oxandrolone 10 mg for 4 months	Weight: ↑ Lean body mass: ↑ 6MWT: ↑
Creutzberg et al, 2003	33/30	♂ moderate to severe COPD	Nandrolone Decanoate: 50 mg for 8 weeks	Lean body mass: ↑ MIP: ↑
Casaburi et al, 2004	23/24	♂ moderate to severe COPD testosterone ≤ 400 n/dl	Testosterone 100 mg/week for 10 weeks	Lean body mass: ↑ Peripheral muscle strength: ↑ VO_2 and W peak:↑
Svartberg et al, 2004	29/0	Men moderate to severe COPD	Testosterone 250 mg every 4 weeks for 26 weeks	Lean body mass: ↑ Improvement in quality of sex life

COPD: chronic obstructive pulmonary disease; BMI: body mass index; MIP: maximal inspiratory pressure; 6MWT: 6-minute walk test; =: without alterations; : increase; decrease; W: workload; VO2: oxygen consumption

the dosage or by discontinuing the medication and administering diuretics.

In another study, 50 mg of intramuscular nandrolone decanoate was administered every 2 weeks for 8 weeks in a group of men with moderate to severe COPD (FEV_1 = 38 ± 17% of predicted), accompanied by pulmonary rehabilitation.[17] In relation to a control group, the supplemented patients presented greater muscle mass gain. However, the improvements in muscle function, exercise capacity and state of health were similar in both groups.

In a placebo-controlled study, 100 mg of testosterone was administered to men with moderate to severe COPD (FEV_1 = 60% of predicted) who presented low testosterone levels (400 g/dl).[18] The authors observed greater increases in lean body mass and muscle strength in the group that received supplementation and training in relation to a group that received testosterone only. The magnitude of the lean body mass increase observed in this study was superior to those described in previous studies,[14-16] probably because the dose of anabolic steroid was six times higher.

In a recent study, 250 mg of testosterone were administered to men with moderate to severe COPD (FEV_1 < 60% of predicted) every 4 weeks for 26 weeks, without rehabilitation intervention. There was an increase in lean body mass, a decrease in fat mass and improvement in the quality of the sex life in the supplemented group in relation to the placebo group.[19]

The correlation between reduction of muscle mass and mortality in patients with COPD[6] could justify the use of steroids in this population, since supplementation with these substances has been found to be efficient in increasing body weight and muscle mass.[14-19] However, before initiating this therapy, we have to ensure that there is no prostatic neoplasm or significant liver disease since both processes can be accelerated by the supplementation.

In addition, it should be borne in mind that most

Chart 2 - Main characteristics of studies that used human growth hormone in patients with COPD

Author, year	N patients Controls	Inclusion criteria	Supplementation	Results
Suchner et al, 1989	6/0	moderate to severe COPD with weight loss	rhGH: 0.03 mg/kg/day for 4 days, followed by 0.06 mg/kg/day for 4 days	BEE:↑ Oxidation of fats: ↑ Oxidation of protein and glucose: ↓
Pape et al, 1991	7/0	FEV_1< 70% predicted FEV_1/FVC < 0,65 ideal weight ≤ 90%	rhGH 0.05 mg/kg/day for 3 weeks	Nitrogen Balance: ↑ Body Weight: ↑ MIP: ↑
Burdet et al,	8/8	FEV_1/FVC ≤ 70% ideal weight ≤ 90%	rhGH 0.15 IU/kg for 3 weeks	Lean body mass: ↑ Peripheral Respiratory Muscle Strength: = 6MWT: =

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; rhGH: recombinant human growth hormone; MIP: maximal inspiratory pressure; BEE: basal energy expenditure; 6MWT: six-minute walk test; =: without alterations; increase; decrease

studies in which the use of anabolic steroids was combined with physical training used endurance exercises,[14-15,17,19] and only one study involved strength training.[18] Therefore, there are insufficient data in the literature to recommend a specific type of physical training to be combined with supplementation, although it is reasonable to suppose that the use of strength training is more appropriate since it would tend to magnify the possible hypertrophic effects on muscle. It is also important to observe that it is often necessary to previously adjust eating habits or energy supplementation in order to optimize the treatment.

More randomized and placebo-controlled clinical trials are still needed in order to evaluate the long-term effects of the use of anabolic steroids combined with physical training.

CREATINE

Creatine is a nutrient found in foods such as fish and meat and can be endogenously synthesized from other amino acids (glycine, arginine and methionine) found in the liver, kidneys and pancreas.[20-21] The majority of the creatine found in the body resides in the skeletal muscle in the form of phosphocreatine. Phosphocreatine is the first energy reserve depleted during activities of high energy demand that vary from ten seconds to approximately one minute.[22] However, its stores are resynthesized within a few minutes, which makes it important in intermittent exercises.[20]

Creatine supplementation has been often used by athletes. However, recent evidence indicates that creatine can be useful in the treatment of diseases, mainly those that result in atrophy and muscle fatigue.[22] Another relevant aspect that would justify the use of creatine in patients with COPD is that this population presents redistribution of types of muscle fibers, with predominance of type II fibers,[23] which are characterized by rapid contractions and present greater anaerobic capacity than do type I fibers. Studies reveal that type II fibers use more phosphocreatine during exercise.[20] Therefore, creatine supplementation, together with physical training, can be a valid alternative means of increasing exercise tolerance.

In a randomized, double-blind, placebo-controlled study, the effect of creatine supplementation was evaluated in 26 patients with moderate to severe COPD.[24] The patients were submitted to endurance and strength training of the lower limbs for 12 weeks. The authors found no statistically significant differences between the groups regarding exercise capacity and muscle strength. However, this study was only published in form of abstract.

In a recent randomized, double-blind, placebo-controlled study, the effect of creatine supplementation was evaluated in 38 stable patients with moderate to severe COPD (FEV_1 = 46 ± 15% of predicted).[25] Supplementation was divided into two phases: loading phase (15 g/day for 2 weeks) and maintenance (5 g/day for 8 weeks), the latter

combined with physical training. The authors observed that the use of creatine resulted in increases in lean body mass, strength and peripheral muscle endurance, especially after the addition of training. The results of this study suggests that creatine supplementation may begin to be considered part of the available ergogenic arsenal for lean body mass increase and structural and functional improvement of skeletal muscle in COPD. It is of note that creatine is known to be safe, with few side effects: water retention (in the intracellular compartment), muscle pain and occasional cramps. However, as in other ergogenic therapies, additional follow-up studies are necessary to evaluate the actual long-term benefits of creatine supplementation in COPD.

L-CARNITINE

The metabolite L-carnitine is essential to the transfer of long-chain fatty acids, and of cytosol to the mitochondrial matrix, where ß-oxidation (the oxidation of fatty acids) occurs, resulting in energy production.[26]

Various studies published in the sports medicine literature have demonstrated the ergogenic effect of L-carnitine in improving performance, showing that it increases the oxidation of fatty acids, decreases the rates of muscle glycogen depletion and increases resistance to muscle fatigue. However, the use of L-carnitine for long periods in untrained healthy individuals has not been shown to improve physical performance.[26]

In another study conducted in Brazil, L-carnitine supplementation combined with physical training was evaluated in patients with COPD (FEV_1 < 65% of predicted) for a period of 6 weeks at a dosage of 2 g/day.[27] The authors observed greater attenuation of the heart rate in a supplemented group in relation to an unsupplemented group. In addition, the distance covered in the 6-minute walk test was greater in the group that received supplementation and physical training.

It seems logical to suppose that L-carnitine supplementation should be used preferably in individuals with satisfactory body composition, especially in terms of adipose reserve, since it stimulates the use of fat as substrate. As with the other substances, further studies of L-carnitine are needed in order to determine its potential benefits in patients with COPD.

BRANCHED-CHAIN AMINO ACIDS

The branched-chain amino acids (BCAAs) leucine, isoleucine and valine are primarily metabolized in the skeletal muscle as energy substrate or are used as precursors of the synthesis of other amino acids and proteins.[28] These BCAAs exert a significant influence on the metabolism of glutamine and together serve as an important energy substrate for the brain, kidneys, liver and heart. The increased BCAA concentration in the skeletal muscle reduces glutamate dehydrogenase activity, thereby limiting glutamine degradation.[28] Intracellular glutamate plays a central role in the preservation of high-energy phosphates in muscle,[29] and its low intramuscular levels have been correlated with early lactic acidosis during exercise.[30] Infusion with BCAAs stimulates synthesis and decreases protein degradation, thereby regulating muscle renovation.[31] During prolonged exercises, BCAAs can constitute an oxidative substrate for the skeletal muscles. Under conditions of relative energy shortfalls, such as those induced by sepsis, trauma and hypoxia, the BCAA metabolism is accelerated in the skeletal muscle.[28]

In studies evaluating the profile of amino acids in the plasma and skeletal muscle of patients with COPD, decreased BCAA levels were observed in the skeletal muscle of patients with predominance of emphysema[32] and in the plasma of patients with body weight at 90% of the ideal.[33] The rationale behind the use of BCAAs in COPD is also based on the observation that its oral administration in healthy elderly individuals stimulates the transfer of amino acids to the muscle, which has been correlated with protein synthesis,[29] especially when ingested before or immediately after exercise.

To date, there have only been two studies related to the use of BCAAs in patients with COPD.[34-35] In one of those studies, the effects of nutritional supplementation with a BCAA (1.5 times the baseline energy expenditure for a year) were examined in undernourished patients with COPD.[34] The authors reported improvement in the nutritional state, as well as increased respiratory muscle function and improved quality of life. However, because this study was not published in English, it was not possible to analyze the inclusion criteria, drop-out rates, quality of life improvement, supervised versus unsupervised ingestion of the BCAAs and methods of evaluating respiratory muscle strength.

The other was a nonrandomized study using a BCAA at the dosage of 1 lU/7 kg for 5 weeks in a group of patients with COPD.[35] There was improvement in the peak oxygen consumption and maximum load in the groups studied, although the difference between the groups was not statistically significant. The authors observed decreased hypoxemia at rest and hypercapnia between the beginning and the end of the study in the supplemented group. However, there was no mention of whether the patients were hospitalized or not. Therefore, the improvement in their blood gas analysis results could be due to the recovery of clinical stability rather than, as was speculated by the authors, to the direct effect of the BCAAs on the respiratory centers or on the ventilation/perfusion ratio.

In the few studies that discuss the use of BCAAs in patients with COPD, the quality of the methodology was poor. However, there is a theoretical basis for further investigation of these substances in order to evaluate their possible benefits in these patients.

GROWTH HORMONE

The human growth hormone (hGH) is a polypeptide composed of 191 amino acids released by the hypophysis resulting from certain specific physiological stimuli. Through techniques of genetic engineering, it is possible to obtain its synthetic form, recombinant hGH (rhGH). This substance can accelerate the oxidation of fatty acids and increase the capture of amino acids, in addition to exerting a diabetogenic effect secondary to the decreased transfer of glucose through the cellular membrane. Other rhGH-related side effects include peripheral edema, hypothyroidism and gynecomastia.[36]

The hGH stimulates the liver to produce insulin-like growth factor 1, a molecule that binds to plasma proteins. This growth factor is the most important anabolic mediator of hGH[37] and plays a central role in regulating metabolism, as well as in cell proliferation and differentiation[38] (Figure 2). Therefore, the use of hGH has potentially benefits in COPD (Chart 2).

Some authors have evaluated the effect of rhGH in patients with advanced COPD (FEV1 = 29 ± 6% of predicted) via subcutaneous administration (30 mg/kg/day for four days, and later on 60 mg/kg/day for four more days), in 6 patients with weight loss who were receiving parenteral nutrition.[39] The administration of the rhGH was accompanied by increased baseline energy expenditure and oxidation of fats, in addition to decreased glucose oxidation. An improvement in nitrogen balance, which is a potentially relevant effect for patients with low body weight, was observed.

Other authors[40] analyzed the effects of rhGH supplementation (0.05 mg/kg/day of subcutaneous administration for 3 weeks) in 7 patients with COPD (FEV_1 < 70% of predicted) and low body weight (< 90% of ideal weight).[41] There was significant weight gain and improved nitrogen balance. In functional terms, respiratory muscle strength, evaluated by maximal inspiratory pressure, increased by an average of 33% in 6 patients and decreased by 8% in 1. There were no changes in respiratory muscle endurance.

In another study,[42] the effects of rhGH administration (0.15 lU/kg/day of subcutaneous administration for 3 weeks) was evaluated in 16 stable patients (FEV_1 < 70% of predicted and body weight < 90% of ideal).[41] The authors observed an increase in muscle mass, although without any accompanying increase in respiratory muscle performance or exercise capacity. Secondarily, there was increase in the baseline energy expenditure and an elevation of the metabolic rate (oxygen consumption and production of carbon dioxide) attributed to the thermogenic effect of rhGH, in addition to the increase in protein renovation and lipolysis.

The effects of rhGH on the functional capacity of patients with COPD are controversial and should be carefully analyzed due to the reduced number of publications, lack of control groups and isolated (without physical training) use of ergogenic therapy.[39-40] In addition, the studies were carried out for a short period of time (approximately 3 weeks), showing acute alterations in metabolism and muscle strength. Therefore, the long-term effects of rhGH administration remain unknown. Another aspect to be explored in future studies is the cost-effectiveness ratio, since rhGH supplementation is expensive and, as previously stated, its clinical benefits have yet to be demonstrated. These aspects, together with the limitation of subcutaneous administration, can explain why no studies of rhGH use in COPD have been published in the last eight years.

CONSENSUAL RECOMMENDATIONS

Considering the impact that the reduced muscle mass seems to exert on morbidity and mortality in patients with COPD, relatively few controlled randomized studies of ergogenic interventions have been carried out. A review of the literature available allows us to suggest that, among the ergogenic supplements evaluated, anabolic steroids, used in appropriate doses and for a limited period of time, hold the most promise as a treatment for COPD. Preliminary evidence also shows good results with the use of creatine and L-carnitine and, to a lesser degree, with BCAAs. The use of rhGH in Brazil seems to be limited by the high cost and by the fact that it requires parenteral administration.

Ergogenic supplementation can be added to the conventional treatment of advanced COPD in the following situations: patients with muscle depletion (lean body mass index = 16 kg/m2 for men and = 15 kg/m^2 for women)[43] or with body weight lower than 90% of ideal weight, according to the Metropolitan Life Insurance standards[41]; patients with weight loss greater than 10% of their usual weight over a six-month period or greater than 5% of their weight in the preceding month[29]; patients in which eating is found to be insufficient, according to information obtained through questionnaires,[44] in relation to the baseline energy expenditure calculated through predictive equations[45] or through indirect calorimetry.[46] Finally, due to the modulatory effect of the use of corticosteroids in response to treatment with nutritional supplementation, the use of ergogenic supplements can be useful in patients who make use of these drugs regularly.

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