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**Impact of nutritional status on body functioning in chronic obstructive pulmonary disease and how to intervene**

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**Abstract****Purpose of review**

Chronic obstructive pulmonary disease (COPD) is the fifth cause of mortality in the world. This article reviews diet as a risk or protective factor for COPD, mechanisms of malnutrition, undernutrition consequences on body functioning and how to modulate nutritional status of COPD patients.

**Recent findings**

Different dietary factors (dietary pattern, foods, nutrients) have been associated with COPD and the course of the disease. Mechanical disadvantage, energy imbalance, disuse muscle atrophy, hypoxemia, systemic inflammation and oxidative stress have been reported to cause systemic consequences such as cachexia and compromise whole body functioning. Nutritional intervention makes it possible to modify the natural course of the disease provide that it is included in respiratory rehabilitation combining bronchodilators optimization, infection control, exercise and in some patients correction of hypogonadism.

**Summary**

Diet, as a modifiable risk factor, appears more as an option to prevent and modify the course of COPD. Reduction of mechanical disadvantage, physical training and anabolic agents should be used conjointly with oral nutrition supplements to overcome undernutrition and might change the prognosis of the disease in some cases. Major research challenges address the role of systemic inflammation and the best interventions for control it besides smoking cessation.

**Keywords:** Nutrition disorders, COPD, inflammation, pulmonary rehabilitation, enteral feeding, oral nutrition supplement, anabolic agents, diet

## 1. Introduction

Nutritional status has been associated with respiratory function in COPD with complex interplays between environmental and genetic factors (Fig. 1) [1•]. Studies have shown that malnutrition served as negative prognostic factor in COPD. Conversely, diet could be a protective or a harmful factor regarding the risk of incident COPD and modifying factor in established disease [2-4]. The question is how we could intervene with nutritional factors to improve prognosis. This review will discuss diet as a risk factor in COPD, mechanisms of malnutrition, consequences of undernutrition on body functioning and how to modulate nutritional status of these patients.

## 2. Diet as a risk factor for COPD

Cigarette smoking is the most important risk factor for COPD, but up to one third of patients with COPD have never smoked [5]. These suggest that other factors, such as diet, also are involved. In the last decade, there has been a growing interest in identifying foods related to lung function or COPD symptoms [5,6,7••]. Nutritional epidemiologists propose to assess overall diet instead of the individual foods or nutrients due to interaction between nutrients [8]. This approach has been used in three recent studies which has used dietary patterns to assess diet in relation with respiratory phenotypes [6,7••,9].

Among the Chinese Singaporeans, a 'meat-dim sum' pattern (meat, dim sum foods, and noodle dish) was associated with an increased risk of incident cough with phlegm [9]. In both a large cohort of US men and US women, a "prudent" pattern (high intake of fruits, vegetables, fish and whole grain products) was associated with a decrease risk of newly diagnosed COPD whereas a Western pattern (high intake of refined grains, cured and red meats, desserts and French fries) was associated with an increase of COPD [6,7••].

Most investigations have focused on the possibility that fruits and vegetables exert beneficial effects on lung health and a very little attention has been paid to other foods or nutrients. Recently, it

has been suggested that dietary fibre was independently associated with better lung function and reduced prevalence COPD [10,11]. Previous studies have mostly focused on the potentially protective effects of foods rich in antioxidants, and not on foods with a potential deleterious effect. However, it was recently reported both in three longitudinal surveys [7••,12,13] and in a cross-sectional survey[14] that frequent consumption of cured meats was associated with higher prevalence and incidence of COPD. All these studies provide additional support to the hypothesis that diet, a modifiable risk factor, is associated with respiratory diseases. Nutritional epidemiology may play an important role in advancing our understanding of the relevant pathophysiological mechanisms involved in the development and progression of respiratory diseases.

### **3. Epidemiology and mechanisms of nutritional depletion in COPD**

Malnutrition in COPD is one of negative predictive factors and mechanisms of nutritional depletion are multifactorial processes that will be described in the next following paragraphs.

#### **3.1. Epidemiology**

Weight loss in COPD was already recognized as a clinical finding and it is more frequent in emphysematous patients as contrary to the blue bloaters [15]. The prevalence of nutritional depletion was about 20-35% in outpatients COPD and up to 70% in patients with acute respiratory failure or in patients awaiting a lung transplantation [4,16-18].

#### **3.2. Mechanisms of nutrition depletion**

Nutrition depletion occurs by including several factors such as energy imbalance, disuse atrophy of the muscles, hypoxemia, systemic inflammation, oxidative stress and hypogonadism in some patients.

##### **3.2.1. Energy imbalance and metabolism changes**

The largest component of energy expenditure (EE) is the basal metabolic rate (BMR), which is the energy needed for basic processes of life and it accounts for 60-70% of total daily EE [19]. Increased energy expenditure due to mechanic disadvantage, metabolic inefficiency with some fibre-

type shift in skeletal muscle from type I to type II, together with systemic inflammation may be determinants of an hypermetabolic state that may not be balanced by dietary intake [20••]. In COPD patients, resting energy expenditure (REE) has been reported to be 15–20% above predicted values due to the increased energy required for breathing [21,22]. Total daily expenditure was also higher in COPD patients compared to healthy subjects and it may be caused by increased level of non-resting daily expenditure [23]. Energy expenditure changes due to impaired mechanical efficiency may be partially reversed by reducing hyperinflation with medication, breathing techniques or lung volume reduction. This could reduced oxygen cost for breathing and increased oxygen availability which favours carbohydrate metabolism and recovery in body composition with lower fat and and higher fat-free masses [24-26].

Chronic obstructive lung disease may induce insulin resistance and changes glucose metabolism [27]. Data from the Third National Health and Nutrition Examination Survey showed that impaired glucose regulation was associated with impaired lung function [28]. Glucose plasma concentrations were similar in non-hypoxemic COPD patients and healthy subjects. Abnormal glucose metabolism may be a risk factor for cardiovascular disease and type II diabetes in COPD [29].

Some data showed that increased proteolysis in cystic fibrosis (CF) patients was related to impaired glucose tolerance due to resistance to the anabolic effects of insulin on proteolysis [30]. High catecholamine level in COPD may induce hypermetabolic response which causes increased EE and muscle-protein catabolism [31,32]. These findings suggested some role of insulin resistance in FFM (fat free mass) depletion.

COPD patients often have dyslipidemia related to metabolic syndrome (abdominal obesity, increased triglycerides, dyslipidemia) and it is due to some changes in lipid metabolism. [33]. Jackobsson et al found a decrease in lipolysis and increased glucose levels in patients with advanced COPD with chronic respiratory failure, signaling a role of insulin resistance in the reduction of lipolysis

[34]. These findings suggested that FM (fat mass) relatively preserved or increased due to decrease lipolysis.

### **3.2.2. Disuse atrophy of muscles**

Patients with very severe COPD are very inactive as compare to healthy people of the same advanced age [35]. Several studies have shown that these patients have an increased protein breakdown pathways, in particular the NF-kB-activated ubiquitin/proteasomal pathway and apoptosis [36].

### **3.2.3. Hypoxemia**

It has been suggested that the hypoxemia of COPD is one causative factor for cachexia. Hypoxemia may increase the generation of ROS and TNF- $\alpha$  which in turn may give rise to inflammatory changes leading to cachexia [37]. It may stimulate the sympathetic nervous system and this has been shown to produce systemic inflammation [38].

### **3.2.4. Systemic inflammation and oxidant stress**

Systemic inflammation has important metabolic consequences and become the primary focus of research into the genesis of cachexia in COPD. The molecules receiving the greatest amount of attention are TNF- $\alpha$ , IL-1 $\beta$ , IL-6, CRP, and ROS and reactive nitrogen species (see ref.20 for review) and may play a role in cachexia. COPD has been proposed in this context a new syndrome called “chronic systemic inflammatory syndrome” including at least 3 out of 6 following factors: age older than 40, more than 10 year-smoking history, symptoms and pulmonary functions compatible with COPD, chronic heart failure, insulin resistance, and increased plasma CRP [39••,40]. There may be also a link between inflammation and leptin levels. Nevertheless, major gaps persist related to environmental and genetic factors underlying cachexia susceptibility, to sequential molecular steps [20••].

### **3.2.4. Hypogonadism**

There is evidence that insufficiency of one or more of three hormones may contribute to cachexia. Creutzberg et al have provided an overview of endocrine factors in COPD [41]. Low levels

of circulating hormones do not prove cause and effect in cachexia in COPD. Inversely, anabolic hormones replacement may have a role in selected patients as reported in various publications.

#### **4. Impacts of malnutrition in COPD**

Impact of malnutrition in COPD on body functioning will be emphasized on body composition, on lung parenchyma, respiratory function, respiratory mechanics, physical capacity, and also morbidity and mortality.

##### **4.1. Body composition**

Patients with COPD are known to be generally underweight and have reduced FFM as showed by several studies [42,43]. Study by Sergi et al showed that COPD patients had a lower FFM as compared to healthy subjects (38% versus 31%) [42]. In a large out-patient population of patients with COPD in Netherlands, they found prevalence of normal BMI and low FFMI was 15%, and of low BMI and low FFMI 11% [17].

##### **4.2. Lung parenchyma, respiratory function and respiratory mechanics**

Massaro et al described loss of pulmonary alveoli in calorie restriction and regenerated after *ad libitum* refeeding [44]. Undernutrition led to lung and chest wall mechanical changes, such as distorted structure of diaphragm and intercostals, reduction of surfactant and decrease in elastic fibre content of pulmonary parenchyma [45]. Inspiratory muscle weakness and maximum inspiratory pressure generation was an independent determinant of survival in severe COPD [46]. The diaphragm as a main inspiratory muscle is suffered from muscle protein degradation and loss of contractile protein [47]. In study by Cano et al the degree of respiratory impairment (FEV<sub>1</sub>, FVC and 6-min walking test) was correlated with nutritional status especially FFM [48].

##### **4.3. Physical capacity**

Daily physical activity can be considered as “the totality of voluntary movement produced by skeletal muscles during everyday functioning” [49]. It is widely known that in patients with COPD,



lower levels of physical activity in daily life are related to higher risk of hospital readmission and shorter survival. The effect of skeletal muscle dysfunction contributes to declining body functioning as we defined as physical activity. Physical activity greatly influences patient outcomes because level of physical activities was shown to predict the risk for hospitalization [50,51]. Overall impairment of body functioning can be described in Figure 2 as adapted from International Classification of Functioning (ICF) [52].

#### **4.4. Morbidity and mortality**

Mortality of COPD patients and occurrence of acute exacerbation requiring hospitalization are higher in underweight patients. During hospitalization, COPD patients are most likely to lose weight because of the higher metabolic demand due to increased ventilatory disadvantage or infection and underweight patients also had a higher risk of new exacerbation [53]. Landbo et al described that in mild to moderate COPD the best prognosis was found in normal weight or overweight subjects, whereas in severe COPD, overweight or obese patients were associated with a better survival. These patients may be somehow protected from weight loss because of higher energy reserves [54].

### **5. How to intervene**

The questions on how to intervene in these patients exist and we will discuss how and possible methods to modify disease progression or prognosis.

#### **5.1. Nutrition requirements**

The question on how much we should give nutritional repletion still remains. In the study by Planas et al, it was described that total daily energy intake of REE x 1.3 was preferable than REE x 1.7 in mild stable COPD patients. They found that administration of nutritional supplements, high in proteins, with predominance of carbohydrates over fat, and enriched in antioxidants to achieve total daily defined energy intake in patients in group REE x 1.3 was followed by a significant improvement of body weight, handgrip strength, decrease airflow limitation and increase quality of life [55]. Total

calories being administered as 20% proteins seemed to be the optimal in nutritional supplements for stable malnourished COPD patients. Small portion of carbohydrate and protein-rich supplementation seemed to have an impact on weight gain after 8 weeks when compared to normal size supplements of similar macronutrient composition, probably because many patients still usually took ordinary meals outside the supplementation [56]. High load of portion will compromise diaphragm movement and caused postprandial dyspnea because it will prevent the diaphragm to move easily due to gastric filling pressure [57].

## 5.2. Methods

Metabolic syndrome carries a lot of consequences in managing nutrition in COPD patients because of glucose level, hypertension, atherogenic dyslipidemia or other co-morbidities such as congestive heart failure. Methods that are known for nutritional intervention in COPD patients varied between studies.

### 5.2.1. Oral nutrition supplements

Nutritional support includes food enrichments, oral nutritional supplements, tube feeding and parenteral nutrition.[58] There is limited evidence that wasting COPD patients will benefit only with enteral nutrition as showed by meta-analysis by Ferreira et al[59] and reported in ESPEN recommendations in 2006[57]. **Table I** described some nutritional supplementation studies in COPD patients which were integrated or non-integrated with pulmonary rehabilitation. Refeeding in malnourished COPD patients is not easy and difficult to maintain due to many factors. The 2005 Cochrane Review on nutritional supplementation for stable COPD had some important limitations relative to the small numbers of patients included, 214 in supplement arm *versus* 205 in control group, the non-integration of nutritional intervention in a pulmonary rehabilitation process, the short duration of intervention between 2 weeks to 3 months, and the lack of relevant endpoints to measure the effects of nutrition supplementation as quality of life, body composition or exercise capacity [57,68]. These limitations should encourage larger studies with a multimodality approaches and clinically relevant end-points.

### **5.2.2. Exercise**

Physical training will also have positive effects as anabolic process as it can increase FFM and functional status although it did not directly correlated [69]. Some others studies showed that physical training only will cause negative energy balance because of increase total energy expenditure, but this effect can be overcome by giving supplementation rich in carbohydrate. Glycogen storage is low in muscle of COPD patients and therefore carbohydrate can serve as better energy source [70].

### **5.2.3. Anabolic agents**

Anorexia is one of many factors contributes to cachexia in COPD. The use of appetite stimulating therapy in cachexia COPD patients is now getting more attention [71]. Progestogens (megestrol acetate) can be used to treat anorexia-cachexia. This agent can stimulate appetite and has antagonist effects of pro-inflammatory cytokines [72]. Androgenic hormones has been reported with some successes when combined with exercise, but problems of extra physiologic doses remain [73].

**(Table II)**

### **5.2.4. Multimodality approaches**

A holistic approaches such as the combination of adequate nutritional support with reduction of mechanical insufficiency (with drugs, lung volume reduction, breathing technique), physical activity, anabolic agents or appetite stimulants and non-invasive ventilation will give these patients potential improvements strategy [24,25,79].

### **5.2.5. New tools**

Studies also have shown encouraging effects of *n*-3 polyunsaturated fatty acids (PUFAs) on cytokine release, markers of immune function, on exercise capacity and FFM of COPD patients [80]. Therefore nutrition support with PUFA can be considered to give positive effect for these patients. Oxygen supplementation could reduce dynamic hyperinflation at rest and during or after exercise due to changes in ventilatory pattern [81]. A significant weight gain was observed in malnourished COPD patients after NPPV initiation due to reduce hyperinflation which can help diaphragm to work more

efficiently and avoid dyspnea when eating (gastric filling) [82]. A better knowledge of molecular steps and targets involved in systemic consequences of COPD is of paramount importance to have better treatments. As an example, it appeared that the peroxisome proliferator-activated receptors (PPARs) are involved in cachexia, decreased oxidative muscle metabolism, oxidative stress and systemic inflammation suggesting role for PPARs agonists [83].

### **Conclusion and non-answered questions**

Nutritional depletion has been widely reported in COPD patients. Diet may also play a role both in the development and the progression of the disease. Holistic management for these patients should include nutritional modulation beside reduction of mechanical disadvantage with long-acting bronchodilators, lung volume reduction, physical activity, anabolic agents or appetite stimulants and non-invasive ventilation. Furthermore, metabolic syndrome must be considered in the management of COPD in order to avoid any co-morbidities complication.

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### **Legends of figures**

Figure 1. Gene-environnement interactions on body composition and the risk of COPD

Figure 2. COPD as systemic disease in the context of the International Classification of Functioning, ICF-2, WHO 2001[52,83]

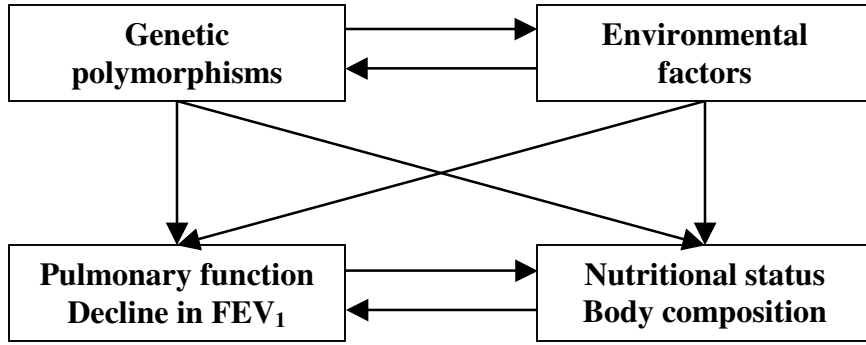


Fig. 1.

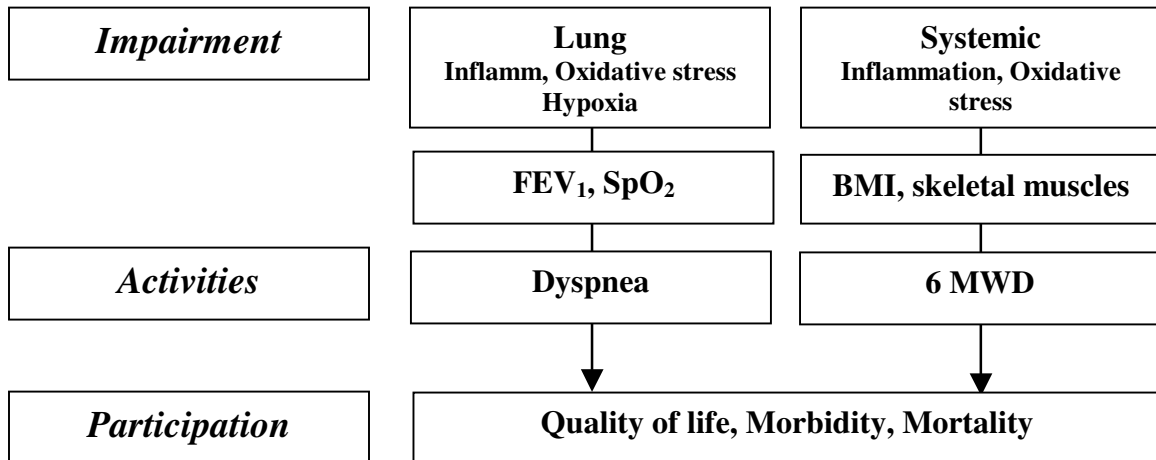


Fig.2

Abbreviations: BMI: body mass index, 6MWT : 6 minutes walking test, FEV<sub>1</sub>%: percentage of predicted FEV<sub>1</sub>



**Table I. Nutritional supplementation studies with more than 2 weeks supplementation in COPD patients, integrated (filled in grey) and non integrated with rehabilitation programme (includes only studies after year 1990)**

<b>Author, year</b>	<b>Patient's characteristics, settings</b>	<b>Study design</b>	<b>n, supplementation group/control, intervention</b>	<b>Judgements criteria <i>Results</i></b>
<b>Faager et al, 2006[58]</b>	COPD patients with FEV <sub>1</sub> < 70% , outpatients	Randomized, double-blind, placebo-controlled study	23, 13/10, creatine supplementation & exercise training	Physical performance, lung function test <i>No significant improvement</i>
<b>Fuld et al, 2005[59]</b>	Moderate to severe COPD, outpatients	Randomized double-blind, placebo-controlled study	38, 20/18, creatine nutritional supplementation, pulmonary rehabilitation	Fat-free mass, peripheral muscle strength and endurance, health status <i>Significant improvement in all parameters, except exercise capacity</i>
<b>Matsuyama et al, 2005[60]</b>	COPD patients FEV <sub>1</sub> < 60%	Randomized, double-blind controlled study	64, 32/32, nutritional support with omega-3 PUFA-rich diets	Leukotriene B4 levels, tumor necrosis factor-alpha and interleukin-8 levels <i>Decreased significantly in the n-3 group</i>
<b>Pison, 2004[61]</b>	Chronic respiratory	3-month	122, 60/62, health education +	6MWD, quality of life, body composition, exercise capacity,

	failure at home, on NIV and/or LTOT	randomized, controlled study, at home	pulmonary rehabilitation + androgens + oral nutritional supplements, 560 kcal/day <i>versus</i> health education alone	exacerbation rate, survival <i>Inclusions completed, results pending</i>
<b>Vermeeren et al, 2004[62]</b>	Nutritionally depleted COPD patients, hospitalized patients	Randomized double-blind, placebo-controlled study	57, Energy and protein-rich nutritional supplements during hospitalization for an acute exacerbation	Body composition, respiratory and skeletal muscle strength, lung function and symptoms <i>No significant improvements in lung function or muscle strength</i>
<b>Steiner, 2003[63]</b>	Nutritionally depleted COPD patients, outpatients	Prospective, controlled study	15, 42 / 43, oral supplementation, 570 kcal / j, pulmonary rehabilitation	Body weight, body composition, quality of life (CRQ), quadriceps muscle forces, hand grip, shuttle test <i>Improvement of shuttle test and quality of life</i>
<b>Creutzberg, 2003[64]</b>	Nutritionally depleted COPD patients, outpatients	Prospective, controlled study	19 / 28, oral supplementation 570 kcal/day, pulmonary rehabilitation	Body weight, body composition, lung function, hand grip, respiratory muscle forces, maximal exercise test, quality of life <i>Improvements of body weight, fat free mass, hand grip, respiratory muscle forces</i>
<b>Rogers, 1992[65]</b>	Malnourished COPD patients, hospitalized then	Prospective, controlled study	Oral supplementation, no pulmonary rehabilitation	Body weight, respiratory muscle forces, hand grip, lung function, 6MWT <i>Improvement of body weight, hand grip, respiratory muscle</i>

	outpatients			<i>forces, 6MWT</i>
<b>Fuenzalida,</b> <b>1990[66]</b>	Nutritionally depleted, hospitalized then outpatients	Prospective, controlled study	9, 5/4, oral supplementation, 1080 kcal/day, no pulmonary rehabilitation	Body weight, anthropometry, immune response <i>Improvement of immunity status</i>
<b>Whittaker,</b> <b>1990[67]</b>	Nutritionally depleted, hospitalized	Prospective, controlled study	10, 6 / 4, nasogastric tube supplementation + 1000 kcal <i>versus</i> + 100 kcal, 16 days, no rehabilitation	Body weight, respiratory muscle forces, hand grip, lung function <i>Improvement of body weight and respiratory muscle forces</i>

Abbreviations: P<sub>Imax</sub>: maximal inspiratory mouth pressure; P<sub>E<sub>max</sub></sub>: maximal expiratory mouth pressure; MVV : Maximal Voluntary Ventilation ;

6MWT : 6 minutes walking test ; REE : Resting Energy Expenditure

**Table II. Effects of anabolic agents in COPD patients integrated (filled in grey) and non-integrated with rehabilitation programme**

Author, year	Patient's characteristics, settings	Study design	n, supplementation group/control, intervention	Judgements criteria <i>Results</i>
<b>Casaburi, 2004[74]</b>	FEV <sub>1</sub> of 60% predicted or less, FEV <sub>1</sub> to vital capacity ratio of 60% or less, outpatients	Prospective, randomized, controlled, double-blind study, rehabilitation in 2 out 4 groups	47, 100 mg/week testosterone enanthate in sesame oil	Body weight, body composition, respiratory muscle function  <i>Significant increased lean body mass</i>
<b>Creutzberg, 2003[75]</b>	FEV <sub>1</sub> < 70% predicted, FEV <sub>1</sub> increase ≤ 10% after inhalation β <sub>2</sub> -agonist, outpatient	Prospective, randomized, controlled, double-blind study  Pulmonary rehabilitation	63, 33/30, 50 mg of nandrolone decanoate IM	Body composition, muscle function, exercise capacity, health status, erythropoietic parameters, laboratory parameters  <i>Improvements in muscle function and exercise capacity</i>
<b>Yeh, 2002[76]</b>	FEV <sub>1</sub> < 50% predicted, FEV <sub>1</sub> /FVC ratio < 70%, weight ≤ 90% ideal body weight, outpatient	Prospective, open-label, 4-month clinical trial	128, oxandrolone, 10 mg bid	Body weight, body composition, spirometry, 6MWT  <i>Significant weight gain</i>

<b>Ferreira, 1998[77]</b>	BMI below 20 kg/m <sup>2</sup> , the maximal inspiratory pressure (P <sub>I</sub> max) was below 60% of the predicted value, outpatient	Prospective, randomized, controlled, double-blind study Pulmonary rehabilitation	17, 7/10, 250 mg of testosterone IM at baseline and 12 mg of oral stanozolol a day for 27 weeks	Body mass index (BMI), lean body mass, anthropometric measures, respiratory muscle strength, and functional exercise capacity <i>Increases in BMI, lean body mass, and anthropometric measures of arm and thigh circumference</i>
<b>Burdet, 1997[78]</b>	FEV <sub>1</sub> /FVC ratio ≤ 70% predicted, FEV <sub>1</sub> increase ≤ 10% after albuterol inhalation, BMI ≤ ideal body weight, outpatient	Prospective, randomized, double blind, controlled study Pulmonary rehabilitation	16, 8/8, subcutaneous injection of 0.15 IU/kg rhGH	Nutritional status, resting metabolism, muscle strength, exercise tolerance, dyspnea <i>Increases lean body mass in underweight patients</i>