Nutritional Support in Respiratory Diseases

Module 38.3

Nutritional support in chronic respiratory failure during home pulmonary rehabilitation

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Learning Objectives

- To learn about the magnitude of the burden of the disease and the systemic involvement of chronic respiratory failure;
- To learn about the interactions and complexity of mechanisms leading to undernutrition with compromise of metabolic active tissues, i.e. skeletal muscles;
- To learn about the integration of nutritional support in pulmonary rehabilitation including exercise training for patients with systemic chronic inflammatory diseases as chronic respiratory failure.

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5. Summary

Key messages

- Chronic respiratory failure due to chronic obstructive pulmonary disease (COPD) is an increasing cause of death, especially in developing countries and will be the third cause of premature deaths by 2030;
- Chronic respiratory failure represent the end-stage of numerous chest disease, among which COPD is the leading cause;
- COPD is considered currently as a systemic disease integrated in a “chronic systemic inflammatory syndrome” combining at least 3 out 6 traits: age > 40, smoking history, symptoms
and function compatible with COPD, chronic heart failure, insulin resistance and increased plasma CRP;

- BMI < 21 is a major risk for death in COPD;
- Prognostic staging of COPD as the BODE index includes BMI, Obstruction, Dyspnea and Exercise Capacity;
- In chronic respiratory failure, systemic inflammation and hypoaemia are the two factors causing respiratory cachexia in genetically susceptible subjects;
- Nutritional intervention alone has not proved its efficacy in terms of physical function, body composition, morbidity or mortality;
- Conversely, nutritional support in the form of oral supplements given as an integral part of a comprehensive program of pulmonary rehabilitation has been shown to have positive effects in terms of body composition, exercise intolerance morbidity and mortality in those patients who gain at nearly 2 kilos in weight.
1. COPD as a common and systemic disease

Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality in the world (1). In 2001, COPD was the fifth leading cause of mortality in wealthy countries and further increases in its incidence/prevalence and mortality rate are expected up to 2030, especially in developing countries (2, 3). COPD represents the most important cause of chronic respiratory failure requiring in long term oxygen therapy (LTOT) apart from bronchiectasis, restrictive disorders and mixed respiratory failure (4). Obesity-hypoventilation syndrome and cystic fibrosis are outside the scope of this review.

Nutritional status has been associated with respiratory function in COPD in a complex manner with interplays between environmental and genetic factors (Fig. 1) (2, 5, 6).

![Figure 1 Gene-environnement interactions on body composition and the risk of COPD](image)

Studies have shown that malnutrition is an independent negative prognostic factor in COPD (7-14). Conversely, diet can be a protective or harmful risk factor for developing COPD, and in the case of established disease may modify its natural history (6).

Chronic obstructive pulmonary disease is associated with an abnormal pulmonary inflammatory response to noxious particles or gases (1). These events induce oxidative stress and imbalance between protease and antiproteases activities (1). Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma leads to the loss of alveolar attachments to the small airways, decreases lung elastic recoil and diminishes the ability to maintain airway opening during expiration (1). It has been recognized that COPD is characterized by local and systemic inflammation with elevated plasma levels of cytokines, such as tumour necrosis factor (TNF-α) and interleukin 6 (IL-6), IL-1β, acute phase proteins such as CRP, reactive oxygen species (ROS), and reactive nitrogen species (RNS) (1, 15-18). These pro-inflammatory molecules may induce a cascade effect and have important metabolic consequences such as pulmonary cachexia syndrome, skeletal muscle wasting, insulin resistance, arterial stiffness, hypertension, endocrinal changes, osteoporosis, depression and other changes (16-20). COPD appears more and more as a systemic disease and it has been proposed that it should be incorporated into a new entity called “chronic systemic inflammatory syndrome” characterised by at least 3 out of 6 following traits: 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 (16, 21).

2. Epidemiology and mechanisms of nutritional depletion in chronic respiratory failure

2.1 Epidemiology

Weight loss in COPD has long been recognised and is more frequent in emphysematous patients as opposed to the blue bloaters or bronchitic patients (22). The prevalence of nutritional depletion is
about 20-35% in outpatient COPD clinics and up to 70% in patients among those with acute respiratory failure or awaiting lung transplantation (14, 23-25). In end-stage respiratory disease of any cause, nutritional depletion is extremely prevalent (4).

2.2 Mechanisms of nutrition depletion

2.2.1 Energy imbalance

The largest component of energy expenditure (EE) is the basal metabolic rate (BMR), which is the energy needed for the basic processes of life at rest, and accounts for 60-70% of total daily EE (26). Weight loss occurs when there is an imbalance between EE and energy intake (27). Besides this imbalance in COPD, it has been suggested that COPD patients are hypercatabolic as a result of increased energy demand during breathing. Increased energy expenditure due to the mechanical disadvantage of breathing with hyperinflated lungs, metabolic inefficiency with some fibre-type shift in skeletal muscle away from type I and towards type II, together with systemic inflammation may all contribute to a hypercatabolic state uncompensated by an appropriate increase in dietary intake (18, 20, 28). In some COPD patients with emphysema and hyper inflation, resting energy expenditure (REE) has been reported to be 15-20% above predicted values due in part to the increased energy required for breathing (29, 30). Total daily expenditure was also higher in COPD patients compared to healthy subjects, caused probably by increased levels of non-resting daily expenditure (31). EE changes due to impaired mechanical efficiency may be partially reversed by reducing hyperinflation with medication, breathing techniques or lung volume reduction (32-35). This could result in increased oxygen availability and a reduction in the oxygen cost of breathing. As a consequence, more physiological conditions which favour carbohydrate metabolism, an increment in respiratory quotient, and recovery in body composition, with lower both fat and higher fat-free masses may be achieved (34).

Chronic obstructive lung disease may induce insulin resistance and changes glucose metabolism (36). On the other hand, data from the Third National Health and Nutrition Examination Survey showed that impaired glucose regulation was associated with impaired lung function (37). Glucose plasma concentrations were similar in non-hypoxaemic COPD patients and healthy subjects. However, glucose metabolism was altered in severely hypoxaemic patients and not corrected by short-term oxygen supplementation (38). Abnormal glucose metabolism may be a risk factor for cardiovascular disease and type II diabetes in COPD (39).

COPD patients often have dyslipidaemia in the context of the metabolic syndrome suggesting that there is an element of altered lipid metabolism. Some data showed that even with FFm loss, FM is relatively preserved or increased (40). Fat oxidation in skeletal muscle was reported to be impaired. Increased nor-epinephrine levels were observed in COPD patients (41) and probably contribute to the increased EE and muscle-protein catabolism (42). Jackobsson et al found a decrease in lypolysis in patients with advanced COPD and chronic respiratory failure. They also found increased glucose levels in patients with chronic respiratory failure suggesting a role of insulin resistance in the reduction of lypolysis (43), which may in turn help to explain the relative preservation of fat mass.

2.2.2 Disuse atrophy of muscles

Patients with very severe COPD are very inactive, and are likely to be more so than healthy people of the same, usually advanced, age (44). Nevertheless this would not explain the 25% prevalence of cachexia in COPD suggesting that inactivity is unlikely to be the only factor involved in cachexia. Several studies have shown that these patients have an acceleration of their protein breakdown pathways, in particular the NF-kB-activated ubiquitine proteasome pathway and apoptosis (45-47).

2.2.3 Hypoxemia

It has been suggested that the hypoxaemia of COPD is a major cause of cachexia by increasing the generation of ROS and TNF-α which in turn may give rise to the inflammatory changes which lead to cachexia (48, 49). Finally hypoxaemia may stimulate the sympathetic nervous system, and this itself has bee shown to produce systemic inflammation (50).

2.2.4 Systemic inflammation and oxidative stress

Systemic inflammation has become the primary focus of research into the genesis of cachexia in

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COPD. The molecules receiving the greatest amount of attention are TNF-α, IL-1β, IL-6, CRP, and ROS and reactive nitrogen species (see ref. 18 for review). There may be also a link between inflammation and leptin levels.

Oxidative stress is greater in COPD patients than in controls and may also play a role in cachexia. Nevertheless, major gaps in our knowledge of the causes of cachexia persist, particularly in relation to environmental and genetic factors and the molecular steps through which these operate.

2.2.5 Hypogonadism
In their review of endocrine factors in COPD, Creutzberg et al have suggested evidence that insufficiency of one or more of three hormones may also contribute to cachexia (51, 52). Low levels of circulating hormones, however, do not prove cause and effect in cachexia in COPD, although anabolic hormones replacement may have a role in selected patients as reported in Table 2.

3. Impacts of malnutrition in COPD

3.1 Body composition
In patients with COPD or chronic respiratory failure, assessment of nutritional status by body mass index (BMI) alone may conceal changes in fat-free mass (FFM) index and depletion of muscle mass (53-55). A normal or high BMI can be associated with FFM depletion and consequent loss of respiratory muscle strength. Analysis of body composition may therefore be of value in COPD patients. Fat free mass index (FFMI) and BFMI (body fat mass index) provide useful information about body compartments, regardless of height (20).

The metabolic syndrome, including abdominal obesity, increased triglycerides, dyslipidaemia, diabetes, and hypertension, is frequent in COPD (56) and has consequences for the management of nutritional support in this group of patients. It is important to avoid exacerbating hyperglycaemia, hypertension, atherogenic dyslipidemia, or other co-morbidities such as congestive heart failure.

3.2 Lung parenchyma, respiratory function and respiratory mechanics
Stein et al reported similarities in lung morphology in starving humans and in patients with emphysema (57). The regulation and molecular basis of pulmonary alveolar regeneration are not well understood. Massaro et al described a loss and regeneration of pulmonary alveoli in calorie restriction, followed by ad libitum re-feeding (58). Starvation was shown to aggravate elastase-induced injury and conversely re-feeding led to the complete recovery of the mechanical properties but to only a partial recovery of the morphometric changes induced by starvation (59). Undernutrition led to lung and chest wall mechanical changes, such as distorted structure of the diaphragm and intercostal muscles, reduction of surfactant and decrease in elastic fibre content of pulmonary parenchyma (60). Inspiratory muscle weakness was one of major clinical findings in patients with COPD and maximum inspiratory pressure generation was an independent determinant of survival in severe COPD (61-63). The main inspiratory muscle, the diaphragm, is exposed to oxidative stress and sarcomeric injury (64), causing muscle protein degradation, loss of contractile protein, and impaired contractile function. All these changes contribute to the respiratory muscle dysfunction characteristic of COPD (60, 65).

3.3 Physical capacity
Physical activity is defined by “any bodily movement produced by skeletal muscles that results in energy expenditure”. Therefore, physical activity in daily life (or daily physical activity) can be considered as “the totality of voluntary movement produced by skeletal muscles during everyday functioning” (44). It is widely known that in patients with COPD, lower levels of daily physical activity are related to a higher risk of hospital readmission and shorter survival. Skeletal muscle dysfunction, resulting from a combination of cachexia and systemic inflammation in COPD, leads to reduced physical activity (66). Using an activity questionnaire, a low BMI has been correlated with lower activity level, (67).

Systemic inflammation, reflected by CRP, is associated with reduced exercise capacity. The level of physical activity, in turn, influences outcome, including the risk of hospitalization (9, 67-69). The overall impairment of body function is described in Figure 2, adapted from the International Classification of Functioning (70).
Figure 2 COPD as systemic disease in the context of the International Classification of Functioning, ICF-2, WHO 2001 (70,71)

3.4 Morbidity and mortality
The mortality of COPD patients and the frequency of acute exacerbations requiring hospitalization are higher in underweight patients. During hospitalization, COPD patients are most likely to continue losing weight because of the higher metabolic demand due to increased ventilatory disadvantage or infection. Underweight patients also had a higher risk of readmission due to further exacerbations (72, 73). Survival analysis of COPD patients supports the hypothesis that low body mass index (BMI) is an independent prognostic factor for poor outcome and that this effect can be reduced by appropriate therapy (74, 75). Landbo et al found that, in mild to moderate COPD, overweight or obese patients were associated with a worse survival. These patients may be protected from weight loss because of their higher energy reserves, but obesity also reduces FEV\textsubscript{1} (7). BMI is also an independent marker of survival in those suffering from other causes of chronic respiratory failure requiring long-term oxygen therapy and/or home mechanical ventilation (9). In another study by Cano et al, the degree of respiratory impairment (FEV\textsubscript{1}, FVC and 6-min walking test) was also correlated with nutritional status especially FFM (4). Vestbo et al (13) suggested that FFMI provided useful information in addition to BMI. These findings suggested that the assessment of FFM should be considered in the routine assessment of COPD (7, 76).

4. How to intervene

4.1 Nutritional requirements
The question of how much we should give to achieve nutritional repletion still remains unclear. In the study by Planas et al, a total daily energy intake of REE x 1.3 was described as preferable to REE x 1.7 in stable patients with mild COPD. They found that the administration of nutritional supplements, high in protein, with predominance of carbohydrates over fat, and enriched with antioxidants to achieve a total daily energy intake of REE x 1.3 was followed by a significant improvement in body weight and handgrip strength, as well as decreased airflow limitation and increased quality of life (77). The optimum proportion of protein to total calories in nutritional supplements for stable malnourished COPD patients seems to be 20%. A protein source with a relatively high amount of cysteine (such as whey protein) seemed more effective in increasing glutathione content (77). Small portions of carbohydrate and protein-rich supplements seem to have a greater impact on weight gain after 8 weeks compared to larger portions of similar macronutrient composition, probably because smaller portions did not reduce intake from normal meals (SPA. Is this what the authors meant?) (78). Large portions, by causing gastric distension, also compromise diaphragmatic movement and caused postprandial dyspnea (78, 79).

4.2. Methods
4.2.1 Orexigen
Megestrol acetate can be used to treat anorexia-cachexia. This agent can stimulate appetite and antagonises pro-inflammatory cytokines (80).

4.2.2 Oral nutritional supplements
The objective of nutritional support is to increase total nutrient intake. Nutritional support includes food enrichments, oral nutritional supplements, tube feeding and parenteral nutrition (81). There is limited evidence that wasting COPD patients benefit from enteral nutrition alone, as showed by meta-analysis by Ferreira et al (82) and reported in ESPEN recommendations in 2006 (79). In this study, there was no evidence to suggest improvements in anthropometric measures or functional exercise capacity among patients with stable COPD (82). Table 1 describes some nutritional supplementation studies in COPD patients which were integrated or not with pulmonary rehabilitation. Re feeding in malnourished COPD patients is not easy and is difficult to maintain due to many factors. The effect of re feeding on peripheral and respiratory muscle function in malnourished COPD patients was first studied by Whittaker et al. They showed that short term re-feeding improved respiratory muscle strength (83). The 2005 Cochrane Review on nutritional supplementation in stable COPD described some important limitations of studies to date, including inadequate numbers of patients, (214 in supplement arm versus 205 in control group), the non integration of nutritional and other interventions in the pulmonary rehabilitation process, the short duration of nutritional support (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 (79, 82). These limitations should encourage larger studies with a multimodal approach and clinically relevant end-points. Moreover, the mechanisms of cachexia need to be better understood in order to design more successful treatment. In this respect, new treatments to achieve better control of inflammation are needed.

4.2.3 Exercise
Physical training may also have positive effects on the protein anabolism, increasing FFM and functional status, although it has not been directly correlated with these parameters in COPD(84). Other studies have shown that physical training causes negative energy balance by increasing total energy expenditure, although this effect can be overcome by giving carbohydrate rich supplements. Muscle glycogen stores are low in COPD patients and carbohydrate may be a better energy source in this respect (85). Although physical training can give positive results, it does not change inflammatory status (86).

4.2.4 Anabolic agents
Anorexia is one of many factors contributing to cachexia in COPD. The use of appetite stimulating therapy in cachectic COPD patients is now getting more attention (28). The use of androgenic hormones has been reported with some success when combined with exercise, but problems of side effects from extra- physiological doses remain (Table 2) (55).

Table 1 Nutritional supplementation studies with more than 2 weeks supplementation in COPD patients, integrated (filled in grey) or non integrated with rehabilitation programme

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patient’s characteristics, settings</th>
<th>Study design</th>
<th>n, supplementation group/control, intervention</th>
<th>Judgements criteria Results</th>
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<tbody>
<tr>
<td>Pison, 2004 (87) in progress</td>
<td>Chronic respiratory failure at home, on NIV and/or LTOT</td>
<td>3-month randomized, controlled study, at home</td>
<td>122, 60/62, health education + pulmonary rehabilitation + androgens + oral nutritional supplements, 560 kcal/day versus health education alone</td>
<td>6MWD, quality of life, body composition, exercise capacity, exacerbation rate, survival Inclusions completed, results pending</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Type</td>
<td>Participants</td>
<td>Design</td>
<td>Intervention</td>
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<tr>
<td>Faager, 2006 (88)</td>
<td>COPD patients with FEV1 &lt; 70%, outpatients</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>23, 13/10, creatine supplementation &amp; exercise training</td>
<td>Physical performance, lung function test</td>
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<tr>
<td>Fuld, 2005 (89)</td>
<td>Moderate to severe COPD, outpatients</td>
<td>Randomized double-blind, placebo-controlled study</td>
<td>38, 20/18, creatine nutritional supplementation, pulmonary rehabilitation</td>
<td>Fat-free mass, peripheral muscle strength and endurance, health status</td>
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<tr>
<td>Matsuyam, 2005 (90)</td>
<td>COPD patients FEV1 &lt; 60%</td>
<td>Randomized, double-blind controlled study</td>
<td>64, 32/32, nutritional support with omega-3 PUFA-rich diets</td>
<td>Leukotriene B4 levels, tumor necrosis factor-alpha and interleukin-8 levels</td>
</tr>
<tr>
<td>Vermeere, 2004 (91)</td>
<td>Nutritionally depleted COPD patients, hospitalized patients</td>
<td>Randomized double-blind, placebo-controlled study</td>
<td>57, Energy and protein-rich nutritional supplements during hospitalization for an acute exacerbation</td>
<td>Body composition, respiratory and skeletal muscle strength, lung function and symptoms</td>
</tr>
<tr>
<td>Steiner, 2003 (85)</td>
<td>Nutritionally depleted COPD patients, outpatients</td>
<td>Prospective, controlled study</td>
<td>85, 42/43, oral supplementation, 570 kcal/j, pulmonary rehabilitation</td>
<td>Body weight, body composition, quality of life (CRQ), quadriceps muscle forces, hand grip, shuttle test</td>
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<td>Creutzberg, 2003 (92)</td>
<td>Nutritionally depleted COPD patients, outpatients</td>
<td>Prospective, controlled study</td>
<td>69/28, oral supplementation 570 kcal/day, pulmonary rehabilitation</td>
<td>Body weight, body composition, lung function, hand grip, respiratory muscle forces, maximal exercise test, quality of life</td>
</tr>
<tr>
<td>Authors</td>
<td>Status</td>
<td>Methodology</td>
<td>Interventions</td>
<td>Outcomes</td>
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<tr>
<td>Rogers, 1992</td>
<td>Malnourished COPD patients,</td>
<td>Prospective,</td>
<td>Oral supplementation, no pulmonary rehabilitation</td>
<td>Body weight, respiratory muscle forces, hand grip, lung function, 6MWT</td>
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<td></td>
<td>hospitalized then outpatients</td>
<td>controlled study</td>
<td></td>
<td>Improvement of body weight, hand grip, respiratory muscle forces, 6MWT</td>
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<td>Fuenzalida,</td>
<td>Nutritionally depleted,</td>
<td>Prospective,</td>
<td>9, 5/4, oral supplementation,</td>
<td>Body weight, anthropometry, immune response</td>
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<td>1990 (94)</td>
<td>hospitalized then</td>
<td>controlled study</td>
<td>1080 kcal/day, no pulmonary</td>
<td>Improvement of immunity status</td>
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<td></td>
<td>outpatients</td>
<td></td>
<td>rehabilitation</td>
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<td>Whittaker, 1990</td>
<td>Nutritionally depleted,</td>
<td>Prospective,</td>
<td>10, 6 / 4, nasogastric tube</td>
<td>Body weight, respiratory muscle forces, hand grip, lung function</td>
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<tr>
<td>(83)</td>
<td>hospitalized</td>
<td>controlled study</td>
<td>supplementation + 1000 kcal</td>
<td>Improvement of body weight and respiratory muscle forces</td>
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<td></td>
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<td></td>
<td>versus + 100 kcal, 16 days, no</td>
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<td>Otte, 1989</td>
<td>Nutritionally depleted,</td>
<td>Prospective,</td>
<td>28, 13/15, oral supplementation,</td>
<td>Body weight, respiratory muscle forces, hand grip, lung function,</td>
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<td>(95)</td>
<td>outpatients</td>
<td>double blind,</td>
<td>400 kcal/day, no rehabilitation</td>
<td>Improvement of body weight and respiratory muscle forces</td>
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<td></td>
<td></td>
<td>controlled study</td>
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<tr>
<td>Efthimiou, 1988</td>
<td>Nutritionally depleted,</td>
<td>Prospective,</td>
<td>14, 7/7, oral supplementation,</td>
<td>Body weight, respiratory muscle forces, hand grip, lung function,</td>
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<tr>
<td>(96)</td>
<td>outpatients</td>
<td>double blind,</td>
<td>no rehabilitation</td>
<td>Improvement of body weight, mass and peripheral muscle forces</td>
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<td>controlled study</td>
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<td>Knowles, 1988</td>
<td>Nutritionally depleted,</td>
<td>Prospective,</td>
<td>25, 13/12, oral supplementation,</td>
<td>Respiratory muscle performance</td>
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<td>(97)</td>
<td>outpatients</td>
<td>double blind,</td>
<td>increased 18 - 26%, no rehabilitation</td>
<td>No significant changes</td>
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<td></td>
<td></td>
<td>controlled study</td>
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<td>Lewis, 1987</td>
<td>Nutritionally depleted,</td>
<td>Prospective,</td>
<td>21, 10/11, oral supplementation,</td>
<td>Body weight, anthropometry, blood gases, MIP, MEP, MVV</td>
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<tr>
<td>(98)</td>
<td>outpatients</td>
<td>double-blind,</td>
<td>500 - 1000 kcal/day oral, increased</td>
<td>No significant changes</td>
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<tr>
<td></td>
<td></td>
<td>controlled study</td>
<td>calorie = 174 ± 17% REE, no</td>
<td></td>
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<td>Abbreviations: MIP: Maximal Inspiratory Pressure; MEP: Maximal Expiratory Pressure; MVV: Maximal Voluntary Ventilation; 6MWT: 6 minutes walking test; REE: Resting Energy Expenditure</td>
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<td>Author, year</td>
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<tr>
<td>Burdet, 1997 (99)</td>
<td>FEV1/FVC ratio ≤ 70% predicted, FEV1 increase ≤ 10% after albuterol inhalation, BMI ≤ ideal body weight, outpatient</td>
<td>Prospective, randomized, double blind, controlled study Pulmonary rehabilitation</td>
<td>16, 8/8, subcutaneous injection of 0.15 IU/kg rhGH</td>
<td>Nutritional status, resting metabolism, muscle strength, exercise tolerance, dyspnea</td>
</tr>
<tr>
<td>Ferreira, 1998 (100)</td>
<td>BMI below 20 kg/m2, the maximal inspiratory pressure (PImax) was below 60% of the predicted value, outpatient</td>
<td>Prospective, randomized, controlled, double-blind study Pulmonary rehabilitation</td>
<td>17, 7/10, 250 mg of testosterone IM at baseline and 12 mg of oral stanozolol a day for 27 weeks</td>
<td>Body mass index (BMI), lean body mass, anthropometric measures, respiratory muscle strength, and functional exercise capacity Increases in BMI, lean body mass, and anthropometric measures of arm and thigh circumference</td>
</tr>
<tr>
<td>Yeh, 2002 (100)</td>
<td>FEV1 &lt; 50% predicted, FEV1/FVC ratio &lt; 70%, weight ≥90% ideal body weight, outpatient</td>
<td>Prospective, open-label, 4-month clinical trial</td>
<td>128, oxandrolone, 10 mg bid</td>
<td>Body weight, body composition, spirometry, 6MWT</td>
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<td>Creutzberg, 2003 (51)</td>
<td>FEV1 &lt; 70% predicted, FEV1 increase ≤ 10% after inhalation β2-agonist, outpatient</td>
<td>Prospective, randomized, controlled, double-blind study Pulmonary rehabilitation</td>
<td>63, 33/30, 50 mg of nandrolone decanoate IM</td>
<td>Body composition, muscle function, exercise capacity, health status, erythropoietic parameters, laboratory parameters Improvements in muscle function and exercise capacity</td>
</tr>
</tbody>
</table>
Casaburi, 2004 (55)  
FEV1 of 60% predicted or less, FEV1 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  
Significant increased lean body mass

4.2.5 Multimodal approaches
Although nutritional support alone is unlikely to be useful in terms of outcome, greater success may come from holistic and integrated approaches combining adequate nutritional support with reduction of mechanical insufficiency (using drugs, lung volume reduction, breathing techniques), physical activity, anabolic agents or appetite stimulants, and non-invasive ventilation (32-35, 79, 101).

4.2.6 New tools
Studies in COPD patients have shown encouraging positive effects of n-3 polyunsaturated fatty acids (PUFAs) on cytokine release, markers of immune function, on exercise capacity, and FFM (102). Oxygen supplementation may also have positive effects on skeletal muscle metabolism in COPD with hypoxaemia (103). It can reduce dynamic hyperinflation in patients with expiratory flow limitation at rest and during or after exercise, due to changes in ventilatory pattern (104). After initiation of NPPV, significant weight gain was observed in malnourished COPD patients, due to reduced hyperinflation, helping the diaphragm to work more efficiently, and prevention of dyspnea when eating (gastric filling) (104, 105). In hypoxaemic COPD patients, oxygen therapy was also reported to improve insulin-sensitivity (106). In order to develop better treatments we need better knowledge of the molecular steps involved and of the systemic consequences of COPD. For example, it appears that the peroxisome proliferator-activated receptors (PPARs) are involved in cachexia, decreased oxidative muscle metabolism, oxidative stress and systemic inflammation, suggesting a possible role for PPARs agonists (107).

5. Summary
Nutritional depletion has been widely reported in patients with chronic respiratory failure. Diet may play a role both in the development and the progression of the disease. Low BMI and FFM are independent poor prognostic factors for survival in COPD patients. Some studies suggest that the negative effect of low body weight can be reversed by appropriate therapy. While giving optimal pharmacotherapy, we should consider holistic and integrated management strategies for these patients giving nutritional support in the context of a comprehensive pulmonary rehabilitation programme. The combination of adequate nutrition, reduction of mechanical disadvantage with long-acting bronchodilators, lung volume reduction, physical activity, anabolic agents or appetite stimulants and non-invasive ventilation in some patients has potential to improve outcome in these patients.

References
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