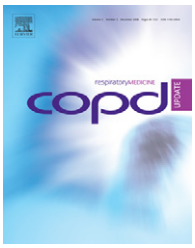

Up date nutritional support for patients with COPD

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ABSTRACT

Chronic Obstructive Pulmonary disease (COPD) is associated with multiple comorbid conditions including ischemic heart disease, peripheral muscular dysfunction, osteoporosis, osteopenia, glaucoma, anemia, anxiety , depression, caquexia and malnutrition. A number of individuals with COPD experience involuntary weight loss as the condition progresses and weight loss, muscle wasting and tissue depletion are commonly seen.

Malnutrition has a negative impact on the clinical course of COPD. The negative impact of malnutrition has led to interest in nutritional assessment and supplementation, alone or in combination with anabolic substances or appetite stimulants, in an effort to improve disease outcome. The effects of nutritional supplementation on weigh gain and anthropometric parameters were small suggesting that oral supplementation alone is of limited efficacy. The studies with anabolic steroids or growth hormone showed improvement in nutritional parameters but no improvement in exercise capacity.

Large randomized trials that include measure of lean body mass, exercise capacity and quality of life should be stimulated.

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder, characterized by progressive airway obstruction and lung hyperinflation, systemic inflammation and increasing frequency and severity of exacerbation. It is largely caused by smoking and may be partially reversible. The pathogenesis and clinical implications of COPD are not restricted to pulmonary inflammation and structural remodeling; COPD is also associated with clinically significant systemic alteration in biochemistry and organ function. The systemic aspects include oxidative stress and altered circulating levels of inflammatory mediators and acute phase proteins. It is now recognized that COPD is associated with multiple comorbid conditions including ischemic heart disease, osteopenia and osteoporosis, glaucoma and cataracts, anemia, peripheral muscular dysfunction, cancer, metabolic syndrome, depression and anxiety, caquexia and malnutrition.[1]

As in other chronic inflammatory conditions, a number of individuals with COPD experience involuntary weight loss as their condition progresses; weight loss, muscle wasting and tissue depletion are commonly seen in patients with COPD.[2]

Attention to the therapeutic implications of weight loss in COPD is relatively recent. These changes were previously considered to be part of the terminal phase of COPD and therefore irreversible. It is time to highlight the clinical importance of depletion of fat and muscle mass due to the fact that 20% of the stable outpatient and 50% of the hospitalized population with respiratory failure will experience them. In advanced COPD, severe weight loss has been referred to as “pulmonary cachexia”.[3] The incidence of malnutrition in patients with COPD depends on disease severity and the criteria and method used to define nutritional status.

1. Implications of chronic obstructive pulmonary-associated weight loss

Malnutrition has a negative impact on the clinical course of patients with COPD, because nutrition and ventilation are intimately related. In the process of respiration, both oxygen

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and nutrients work together to supply the required energy for activities of daily living. In the absence of COPD, malnutrition is associated with a significant impairment of respiratory strength and endurance. Its presence in patients with COPD may aggravate the already existing respiratory muscle dysfunction that is caused by chronic airflow limitation and hyperinflation. COPD patients who lose weight have more dyspnea and less exercise capacity than those who do not, even when their underlying levels of impairment and airflow obstruction are similar[4,5] they also have decreased diffusion capacity and more gas trapping.[4]

Several factors contribute to the impaired respiratory status in malnourished patients with COPD, as malnutrition impairs skeletal muscle function and decreases muscle mass. Loss of respiratory muscle bulk that occurs with severe malnutrition compounds the impaired force generating capacity of the diaphragm. As muscle mass decreases, muscles become overloaded during ventilation. Progressively, muscles become less efficient due to fatigue. Respiratory failure is common as disease and weight loss progresses. Body compositional studies have shown that weight loss is accompanied by significant loss of fat-free mass and that it is specifically the loss of fat-free mass and other measures of muscle mass that are related to impaired skeletal muscle strength and exercise capacity. Interestingly, muscle wasting may occur even in normal weight patients.[6]

The skeletal muscle atrophy that occurs in COPD is specific to fibers IIA/IIX and IIA is associated with disturbed metabolic capacity. Muscular changes are not confined to respiratory muscles; peripheral muscles are also affected, resulting in decreased mobility and a greater risk of falls. Patients with COPD and low body mass index (BMI) have low bone mineral density.[7,8] In a study by Incalzi et al.[9] that evaluated patients with COPD, a BMI of 22 kg/m^2 or less was the only independent factor that was correlated with osteoporosis. Malnutrition decreases respiratory drive, damages lung parenchyma and impairs lung and airways defense mechanism.[10] Malnutrition in patients with COPD has been associated with an increased susceptibility to infection, partially due to impaired cell immunity, reduced secretory immunoglobulin A, decreased pulmonary alveolar macrophage function and increased colonization and adherence of bacteria in the upper and lower airways.[11]

In addition to the effects of malnutrition on the long-term prognosis of COPD, poor nutritional status has been associated with an increased need for mechanical ventilation and mortality in patients hospitalized with an acute exacerbation,[12] or following lung volume reduction surgery.

2. Cause of weight loss and muscle wasting

The weight loss in COPD is probably the result of both a failure of the adaptive response to under-nutrition and inadequate intake for total energy expenditure. Weight loss and the loss of fat mass in particular, may occur if energy requirement is not balanced by dietary intake. Several other pathogenic mechanisms have also been suggested: anabolic hormone deficiency (testosterone, growth hormone, insulin-like growth factor (IGF), leptin), systemic inflammation (tumor necrosis factor (TNF) alpha, interleukin (IL) 1 and 6, C reactive protein, reactive oxygen species), hypermetabolism, tissue hypoxia, muscle atrophy because of disuse, diet-induced thermogenesis, sympathetic activation and accelerated ageing.[13]

Hormonal changes are closely related to overall protein turnover. Insulin, growth hormone (GH), IGFs and anabolic hormones favor protein synthesis, whereas glucocorticoids stimulate proteolysis, especially in muscle tissue. Ghrelin, a naturally occurring growth hormone that releases peptide, has been found to be increased in cachectic COPD patients.[14] High ghrelin levels should promote weight gain, which is not the case in these patients. It is postulated that the high levels could be a result of a feedback loop response to low growth hormone levels.[14]

Systemic inflammation has been a primary focus of research into the genesis of cachexia and weight loss in COPD. Genetic polymorphisms indicate inflammatory cytokines, especially IL-1 B, but IL-6 and TNF-alpha do not show polymorphism in these patients. Early reports of elevated TNF-alpha levels suggested a role for inflammation (ref.), but recent studies have not shown elevated levels of either IL-6 or TNF-alpha, which is somehow disappointing, as both of these molecules have long been regarded as prime candidates in the development of cachexia.[13] Elevated levels of cytokines in cachectic patients could still be an association rather than an indication of cause and effect. There is considerable evidence that this may be important, but there are still many gaps in our present knowledge and it is still not possible to make definitive statement about the role of inflammation.[13]

Chronic inflammation can lead to oxidant stress, which in turn can lead to cell damage and apoptosis. The degree to which oxidative stress occurs in any one patient could vary according to the genes responsible for these phenomena.[15] Agustí et al.[16] found that the number of apoptotic cells increased progressively in biopsy samples of health active subjects, healthy inactive subjects, subjects with COPD and normal BMI and subjects with COPD and low BMI, showing an inverse correlation between BMI and the number of apoptotic cells. These are fascinating findings. However, since this study used only BMI, without direct measure of body composition, and the control subjects were younger than the subjects under study, we do have to interpret them with caution.[17]

A well-conducted review was recently published on this subject. The author concluded that at this point, cachexia cannot be unequivocally attributed to inflammation or to other causes, and more research is needed.[13] It appears that the mechanism for weight loss in COPD is multifactorial and that factors may affect different COPD phenotypes differently.

3. Therapeutic interventions

The negative impact of malnutrition in COPD has led to an interest in nutritional assessment and supplementation, alone or in combination with anabolic substances or appetite stimulants, in an effort to improve disease outcome. Since COPD patients may have elevated metabolism and at the same time be encouraged to exercise, those who suffer from

weight loss, and even some whose weight is stable, should be encouraged to increase their usual nutritional intake. Our aim should be to optimize the treatment of patients who are already underweight, therefore, it is important to detect and reverse involuntary weight loss in order to avoid functional decline.

Nutritional support should start by assessing the patient's dietary habits and adapting their food choice, meal patterns, etc. Because these patients have normal gastrointestinal tracts, oral and in some cases enteral supplements, are recommended first. We should encourage increased dietary intake, more energy-dense foods and optimum timing of meals and snacks in relation to symptoms and activity patterns. Nutritional support should be provided as energy-dense supplements in divided doses over the course of the day to avoid loss of appetite and adverse metabolic and ventilatory effects resulting from a high caloric load.[18]

Daily protein intake should be at least 1.5 g/kg of body weight to allow optimal protein synthesis.[18] When feasible, patients should participate in an exercise program to stimulate the anabolic response and increase lean body mass instead of fat storage. Exercise improves the effectiveness of nutritional support and stimulates the appetite. If weight gain and functional improvement occur, the patient should either continue the current regime or move to a maintenance regimen, depending on results. If the desired response is not achieved, patient compliance should be assessed; if this is not an issue, the patient may require more calories, provided by oral or enteral supplements. Consider the addition of anabolic steroids or other anabolic substances for the next step. However, despite these interventions, some patients will not reach the intended goal, because the mechanism of weight loss may not be reversible with caloric supplementation.[18]

3.1. *Nutritional support*

Given the association between COPD and weight loss, a number of clinical trials have examined the influence of nutritional supplements, either alone or with anabolic substances such as steroids of growth hormone. Single studies revealed that nutritional support in some patients lead to an increase in body weight, fat-free mass, respiratory and skeletal muscle function, exercise tolerance and immune response. Some studies reported an encouraging increase in body weight and improvement in muscle strength in association with oral supplementation, but few reported improvement in dyspnea index or quality of life measures. Trials conducted in outpatient setting are randomized and tend to be of longer duration. Results of a meta-analysis[19,20] and systematic overview have been published.[21]

A total of 10 reports on the effects of nutritional supplements in COPD defined as caloric supplementation lasting at least 2 weeks were selected for inclusion in the original meta-analysis. The effects of nutritional supplementation on weight, arm muscle circumference, triceps skin-fold, 6-min walk test, FEV_1 and respiratory muscle strength were evaluated. The effect size was small. The 95% confidence intervals for all the outcomes included zero. Their actual values were small and unlikely to be clinically significant. The two outcomes (6-min walk test and FEV_1) for which the minimal clinically important difference is known did not exceed this value. All the effect sizes for the outcome measures were homogeneous, indicating that the effect of the intervention was consistent across the studies, irrespective of the duration or the amount of the nutritional support.

After the initial meta-analysis was published, other trials were included[22–24] which did not change the overall results. The literature search and meta-analysis which have been updated at least every 2 years, now includes 14 trials and 487 participants. The 2008 update is underway.

The amount of weight gain in the trials that were longer than 2 weeks was modest at best, with inconsistent improvement in muscle strength, walking distance and quality of life measures. Weight gain, if present, was often due to an increase in fat mass rather than lean body mass. In fact, the majority of trials lacked information on body composition, exercise capacity and health-related quality of life. These results indicated that oral supplementation alone is of limited efficacy in patients with COPD.

Concerns were raised that in the meta-analysis, the authors did not take into account the difference between "failure to intervene" and "failure of the intervention".[25] Obviously, as the trials included mostly outpatients, dietary supervision varied from daily supervision to written instructions supported by 2 weekly visits by a nurse. Although measures of resting energy expenditure (REE) were not always provided, a good approximation was made with the Moore–Angellilo equation ($11.5 \times$ body weight+952), given that most subjects were male. Comparing the approximate REE with the prescribed nutritional protocols, the subjects (both nutritionally depleted and nondepleted) did receive the recommended caloric intake for weight gain ($1.5 \times$ REE).[21] It is possible that individual subjects may not have received the adequate prescribed caloric amount, as patients do tend to decrease their usual intake when receiving supplements, but we cannot believe that it happened to all subjects, and the effect size across the studies was small.

Another meta-analysis of dietary advice for illness-related malnutrition in adults with a variety of clinical backgrounds included some studies with COPD. These results were similarly disappointing. The authors concluded that there was lack of evidence for the provision of dietary advice. Specifically, there were almost no usable data from which to draw conclusions about the effect of dietary advice alone or dietary advice with oral supplements compared to no advice and limited data on advice alone or advice plus supplements compared with supplements alone.[26]

The recent update of this meta-analysis,[27] now including 37 studies and 2714 participants, still shows that it is unclear whether providing dietary advice confers clinical benefit to people with illness-related malnutrition. The limited information available suggests that short-term (up to 3 months) weight gain, grip strength and mid-arm circumference are greater with dietary advice and nutritional supplementation given together rather than when advice is given alone. It is unclear if this is true in the longer term, or whether survival and mortality can be improved.[24,27]

3.2. *Anabolic substances: anabolic steroids and growth hormone*

The use of anabolic steroids for weight gain stemmed from observations that the differences in muscle mass between men and women was attributable to differences of testosterone between the sexes and that hypogonadal patients responded to androgen therapy, with an increase in muscle mass. In normal men, supraphysiological doses of testosterone have been shown to increase muscle size and strength.[28]

Stanozolol, a synthetic derived from testosterone, was used as an anabolic steroid in a small, long-term randomized controlled trial of 27 weeks, in malnourished patient with COPD whose BMI was less than 20 kg/m^2 and maximal inspiratory pressure (PIMAX) was less than 60%. Both study and placebo groups participated in inspiratory muscle exercise training and cycloergometer exercise training. At the end of 6 months, the control and study group differed, with subjects that received stanozolol weighing an average of 2 kg more than the control group. There was significantly different weight, BMI, fat-free mass and anthropometric measures between the groups; however, there was no difference in exercise capacity or respiratory muscle strength. Although stanozolol was used for 6 months, there were no significant side effects,[29] even on prostate size or volume.[30]

In a study with 217 underweight patients with COPD and severe airflow obstructions, Schols et al.[31] reported that nutritional supplements resulted in increased body weight and the addition of nandrolone decanoate resulted in a favorable distribution of muscle mass and a larger improvement in respiratory muscle strength.

Casaburi et al.[32] recently reported increased leg lean mass and strength in men with COPD, who received 10 weeks of testosterone and leg resistance training, but again, there was no improvement in exercise capacity. More recently, their companion biopsy study showed that while either resistance training or testosterone treatment alone exerted positive biochemical and morphometric influences, the greatest impact was seen when they were used together. This included improved morphometric parameters, increased mRNA abundances of all MyHC isoforms and enhanced expression of muscle IGF-I and other components of the muscle IGF system, together with increased myogenin expression, a myogenic regulatory factor (MRF) influenced by IGF-I.[33]

Recombinant human GH (rhGH) was used in a 3-week long, randomized double-blinded trial by Burdet et al., in a small number (16 patients) of underweight patients with COPD. After 21 days, lean body mass increased 2.3±1.6 kg, in the study group and 1.1±0.9 kg in the control group. These gains persisted for 2 months after rhGH was discontinued; however, there were no differences in respiratory or peripheral strength.[34] Casaburi et al.[35] also used rhGH in conjunction with training in COPD patients, and again there was increase in lean body mass, but no improvement in exercise capacity.

More recently, Ghrelin, a growth hormone releasing peptide from the stomach, has been shown to improve body composition and functional capacity in cachectic patients with COPD.[14]

3.3. *Appetite stimulants*

Progestational agents are known to increase body weight and have also been used in COPD. Weisberg et al.[36] used 800 mg of megestrol acetate for 8 weeks. The study group gained 3.2 kg versus 0.7 kg in the placebo group, but the gain was due mainly to an increase of fat mass.

4. Conclusions

Nutritional depletion in patient with COPD is common and has a negative impact on respiratory and peripheral muscle function, contributing to the morbidity and mortality of this condition.

The general assessment of patients with COPD should include weight and the calculation of BMI at each visit. The goal is to try to maintain a reasonable body weight and BMI (between 22 and 27 kg/m^2) and keep serum albumin levels above 3.5 g/dl. Medical treatment of COPD should be maximized; associated co-morbidities should be treated. Spirometry tests, ability to carry out activities of daily living, and the ability to walk specific distances (functional exercise capacity, 6-min walk tests) should be assessed periodically. When indicated, oxygen delivery should be improved through oxygen therapy, when indicated and correction of anemia and cardiac function. It is possible that nutritional therapy should be more individualized and directed to causal factors. Nutritional intervention should be regarded as one component of a multifaceted pulmonary rehabilitation program that also includes exercise.

Weight loss is clearly a marker of disease severity in advanced COPD and it is associated with adverse outcomes independent of lung function. The pathophysiology of weight loss and its consequences are complex and multifactorial, which is perhaps why a clear benefit of nutritional supplementation alone cannot be demonstrated.

Therefore, it is valuable to include management strategies that improve the energy balance to help the patient to gain weight and increase their fat-free mass. Some single trials did show positive results, however, the overall results of studies of nutritional support did not show significant effects. The use of anabolic substances in single trials does seem to increase fat-free mass, mainly when associated with exercise training. Large randomized trials that include measures of lean body mass, quality of life and survival outcomes should be encouraged. The long-term effects of nutritional support and anabolic interventions should be evaluated in multicenter trials. Research has shown that COPD is characterized by a complex variety of metabolic pathways; therefore, further research is needed to clarify the complexity of metabolic alteration related to inflammation, hypoxia, hypercapnia and energetic deprivation. So far, results of published studies in nutritional support show that what we have been doing is still not enough to achieve significant improvement in nutritional outcomes, exercise performance and quality of life. Single trials suggest that improvement in malnutrition may improve survival[37] and may decrease costs.[24] Further research is needed in this extremely stimulating area, where we still have more questions than answers.

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