Nutritional Support in Pulmonary Diseases Topic 38

Module 38.1

Mechanisms of Wasting in Chronic Respiratory Diseases and the Impact of Disease Exacerbations

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Learning Objectives

- To learn about the assessment and prevalence of tissue wasting in COPD;
- To learn about the consequences of weight loss and muscle wasting in COPD;
- To learn about the mechanisms and reversibility of weight loss and muscle wasting in COPD.

Contents

Key Messages

- Emphysematous COPD patients are at particular risk of a negative energy balance and loss of fat mass;
- Hidden loss of fat-free mass is common in COPD, also in earlier disease stages;
- Muscle wasting is associated with impaired functional status and increased risk of mortality in COPD;
- Weight loss has been identified as an important factor in the outcome of acute exacerbations of COPD;
- In the majority of people with COPD, the adverse consequences of weight loss, and in particular muscle wasting, are at least partly treatable by anabolic stimulation (i.e. protein-energy supplementation in combination with tailored exercise);
- Inflammatory modulation may be required to enhance the outcome of nutritional intervention in COPD targeting muscle protein turnover as well as muscle oxidative metabolism.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disorder leading to significant debilitation. While traditionally it has been considered as an irreversible lung disease, there is growing evidence that COPD is a multi-organ systemic disease. Paralleling this development, the interest in weight loss and muscle wasting in the management of COPD has increased remarkably during the past two decades. Involuntary weight loss is well-recognized, as is the fact that a substantial number of patients suffering from COPD become emaciated during the course of the disease. Interestingly, early attempts to classify COPD patients found that body weight might be an important distinguishing factor. This led to the classical description of the pink puffer (emphysematous type) and the blue bloater (bronchitic type). A discriminatory role for body weight and body composition was recently confirmed by two unbiased statistical approaches to classify COPD heterogeneity.
Since weight loss was thought to be an epiphenomenon of severe disease it was not considered as a therapeutic target until the 1980s. However, many studies have convincingly challenged this viewpoint and consistently show that a low body mass index is associated with increased morbidity and mortality independently of disease severity (1, 2). Furthermore, two studies have shown that weight gain is associated with decreased mortality (3, 4) in COPD patients with a body mass index below 25 $kg \cdot m^{-2}$.

2. Prevalence and Consequences of Weight Loss and Muscle Wasting in COPD

2.1 Prevalence

Nutritional assessment in patients with COPD involves assessment of weight loss, body mass index and measurement of body composition to distinguish between changes in fat mass and fat-free mass including lean body mass and bone mass. Weight loss is mostly assessed retrospectively and appears to occur predominantly in advanced COPD of the emphysematous subtype. Assessment of body composition has revealed that differences between the emphysematous and chronic bronchitic subtypes merely reflect a difference in fat mass (5), since depletion of FFM, despite a relative preservation of fat mass, also occurs in chronic bronchitis (5). More recently increasing attention has been given to the increased osteoporosis risk in COPD which is most pronounced in muscle wasted patients.
In stable patients with moderate to severe COPD, a low FFM-index defined as FFM/height^2 <16 kg/m^2 (males) and <15 kg/m^2 (females) has been reported in 20% of COPD out-patients (6), in 35% of those eligible for pulmonary rehabilitation (7) and in 45% of lung transplant candidates (8). Limited data are available regarding the prevalence of FFM depletion in representative groups of mild COPD. The Copenhagen city study showed, in a cohort of 1898 COPD patients during 7 years follow-up, that 10% of patients with mild COPD were underweight while in 25% of normal weight subjects FFMI was lower than the bottom 10th percentile of the general population (9). Note that these authors used a more liberal criterion for the FFM-index in males (i.e. 17 kg/m^2) than previous studies based on recently established normal values for FFM-index in healthy subjects. In summary, the available literature seems to indicate that wasting of fat-free mass precedes wasting of fat mass in

COPD, that loss of fat mass is linked to emphysema and that the prevalence of hidden loss of FFM is already high in mild to moderate COPD.

2.2 Mortality

The relationship between weight and mortality in COPD has been the subject of investigation since the 1960s. In the early years a significant association was reported between weight loss and survival (10). Several more recent retrospective studies using different COPD populations from the USA (1), Canada (11), Denmark (2) and the Netherlands (3) reported a relationship between low body mass index and mortality which was independent of disease severity. Remarkably, in all these studies a decreased mortality risk was observed in overweight patients compared not only to underweight patients but also to normal weight subjects. This observation can be explained by the fact that COPD is not only linked to weight loss but also to a shift in body composition. The normal adaptive response to weight loss is a preferential loss of fat mass to spare loss of the metabolically and functionally active fat-free mass. In contrast, weight loss in COPD is accompanied by significant loss of fat-free mass, out of proportion to the loss of fat mass (7). Studies have also shown that hidden loss of fat-free mass with preservation of fat mass may also occur in normal weight stable COPD patients (7). Furthermore fat-free mass has now consistently been identified, in more than 5 different COPD cohorts as a better predictor of survival than body weight (9, 12, 13).

2.3 Lung Function

The effect of weight loss on lung function has focussed predominantly on ventilatory pump function and has revealed decreased respiratory muscle strength. Similar effects have been shown after weight loss due to anorexia nervosa, controlling for potential effects of altered lung mechanics, i.e. hyperinflation, on respiratory muscle function. Potential effects of weight loss on the lung parenchyma in humans are difficult to explore. It is possible to obtain lung tissue after surgical resection or whole lungs at autopsy in order to study the influence of weight loss on lung structure and function. The presence of coexisting pathological processes which would have led to lung resection or death, however, could hinder investigation of the specific effects of weight loss and nutritional deficiency on lung parenchyma. Developments in high resolution CT scanning allow non-invasive measurement of lung mass and density. Using this technique emphysematous changes were recently detected in patients with severe anorexia nervosa (14). These observations are in line with dramatic reports during the second World War in a Polish Ghetto. In a total of 370 autopsies of Jewish people who were starved to death, 50 cases of emphysema (13.5%) were observed. This is the more remarkable since of the 50 cases, 14 were in individuals under the age of 30 years, and 20 were in persons under the age of 40. The pathological features seen in these mostly young adults were similar to those seen in senile emphysema (15).

2.4 Skeletal Muscle Function and Exercise Capacity

Prominent symptoms of COPD are dyspnoea and exercise intolerance. Independently of pulmonary impairment, skeletal muscle weakness is an important determinant of these symptoms. Body composition studies have shown that skeletal muscle strength is largely determined by skeletal muscle mass in COPD (16, 17, 18). Besides effects on muscle strength, muscle wasting is also a significant determinant of decreased exercise capacity and an altered exercise-induced metabolic and ventilatory response (19, 20). These associations imply that the functional consequences of weight loss are related to muscle wasting as well as to intrinsic alterations in muscle morphology and energy metabolism as will be discussed later. Muscle wasting in COPD is fibre type specific, affecting predominantly the "fast-twitch" type IIx fibres (21). In moderate to severe COPD, wasting of fat-free mass is not only a significant determinant of functional impairment, but also of decreased health related quality of life (22, 23).

2.5 Acute Exacerbations

Many patients with advanced COPD suffer from frequent acute exacerbations. The available literature shows that, during these periods, patients are prone to develop weight loss and deterioration of muscle mass. Recent weight loss was shown to be prevalent in underweight COPD patients prior to hospitalization for an acute exacerbation (24), and weight loss during hospitalisation has been associated with early readmission. Prospective studies have also shown that decline in fat free mass is associated with frequent exacerbations in COPD (26) and that a high proportion of hospitalized COPD patients suffer hidden loss of fat-free mass (24).

3. Mechanisms of Weight Loss and Muscle Wasting in COPD

3.1 Weight Loss and Energy Balance

3.1.1 Energy Expenditure

It is not fully understood why COPD patients become underweight but weight loss and specifically loss of fat mass, are generally the result of negative energy balance and appear to be particularly prevalent in patients with emphysema (5). In contrast to an adaptive decrease in energy metabolism during (semi-) starvation, increased resting energy requirements have been observed in some COPD patients linked to low-grade systemic inflammation (27). Studies in other chronic wasting diseases characterised by hypermetabolism and systemic inflammation (e.g. cancer, chronic heart failure, acquired immunodeficiency disease syndrome (AIDS)) have shown an adaptive decrease in activity-induced energy expenditure so that daily energy expenditure is normal. In contrast, elevated activity-induced and total energy expenditure has been found in free-living ambulatory COPD patients (28). The cause of this disease-specific increase in energy metabolism is not yet clear. A decreased mechanical efficiency of leg exercise has been described that could result from a decreased efficiency of skeletal muscle energy metabolism. Furthermore some studies report an increased oxygen cost of respiratory muscle activity due to lung hyperinflation. An obvious choice to improve energy balance might therefore be to decrease

energy expenditure, although there is ample evidence to show that exercise training is a key component of pulmonary rehabilitation to improve limited functional abilities and to maintain an active lifestyle.
Since COPD patients may have an elevated energy metabolism and should at the same time be advised to increase exercise, restricting energy output, while theoretically desirable from the point of view of energy balance, is likely to be counterproductive in terms of clinical benefit. This implies that COPD patients who suffer from weight loss, and even some weight stable patients, should be encouraged to increase their apparently normal energy intake in order to regain or avoid losing further weight, particularly muscle mass, and to maintain or improve functional ability. Besides treating patients who are already underweight, it is important to adopt a preventive strategy by detecting and reversing nutritional impairment at an early stage before functional decline has set in.

3.1.2 Dietary Intake

Several factors may limit dietary intake in advanced COPD. Dyspnoea and fatigue are prominent symptoms that may affect appetite, particularly during acute exacerbations of the disease (29). Arterial hypoxaemia is also associated with weight loss and decreased dietary intake (24). There is increasing evidence that, besides local upregulation of inflammatory processes in the lung, COPD is characterized by an elevated systemic inflammatory response as reflected by elevated concentrations of pro-inflammatory cytokines and acute phase proteins in peripheral blood (30-32). As in other chronic inflammatory diseases, weight loss has specifically been associated with increased markers of TNFα and soluble TNF receptors (33, 34). These and other inflammatory cytokines have been shown to increase circulating leptin. Leptin, a 167 amino-acid protein synthesized and secreted by white adipose tissue, is a component of a lipostatic signalling pathway that alters energy balance by central and peripheral mechanisms. Administration of leptin in animals results in a reduction in food intake and an increase in energy expenditure. These effects seem to be mediated by a leptin-induced decrease in the hypothalamic biosynthesis and release of neuropeptide Y, a hormone that potently stimulates appetite and food intake and reduces energy expenditure. In patients with emphysema a positive correlation between leptin and the soluble TNF receptor 55 has been shown that could theoretically affect dietary intake (35).
Substrate oxidation and gas exchange through ventilation are intrinsically related. Theoretically therefore, meal-related dyspnoea and impaired ventilatory reserves suggest that it might beneficial to reduce the energy and particularly the carbohydrate content of nutritional supplements used in respiratory patients. Earlier studies indeed showed adverse effects of a carbohydrate-rich energy overload on carbon dioxide production and exercise capacity (36) but these results were not confirmed when using a normal energy load (37). In fact, in some cases, there was even an improvement in lung function and the sensation of dyspnoea using a carbohydrate-rich rather than a fat-rich supplement (38). The effectiveness of nutritional supplements in increasing overall intake, without any concomitant reduction in normal food intake, may be limited by their frequency and volume as well as their timing in relation to meals and other daily activities (39, 40).

3.2 Muscle Wasting and Protein Balance

Wasting of muscle mass is due to an impaired balance between protein synthesis (anabolism) and protein breakdown (catabolism). Besides nutritional abnormalities and physical inactivity, altered neuro-endocrine responses and the presence of a systemic inflammatory response may contribute to a negative protein balance in chronic diseases. From a therapeutic perspective it is important to know the relative contribution of these factors to altered protein synthesis and protein breakdown respectively. While increased dietary intake can compensate for elevated energy requirements and *vice versa*, uncontrolled protein breakdown cannot be overcome by increasing protein synthesis alone.

3.2.1 Protein Metabolism

Several studies in COPD and other chronic wasting disorders have investigated the effects of pharmacological anabolic stimuli to promote protein synthesis, including anabolic steroids, growth hormone and insulin-like growth factor. Most studies in COPD were able to document a modest but significant gain in muscle mass after such interventions (41, 42) illustrating that in some patients, stimulation of protein synthesis is an effective therapeutic strategy. No studies have yet specifically investigated the ability of nutritional *modulation* of protein synthesis or protein breakdown rates to induce or enhance muscle weight gain. Optimising protein intake and essential amino acid intake may not only stimulate protein synthesis *per se*, but also enhance the efficacy of anabolic drugs (43) as well as physiological stimuli such as resistance exercise (44). Protein requirements in COPD patients and many other chronic diseases are not well established. In normal weight COPD patients, whole body protein synthesis and breakdown rates were elevated compared to a well-matched healthy control group (45). A potential explanation for this elevated protein turnover is thought to be enhanced acute phase protein synthesis, associated with low-grade inflammation. This is balanced by increased amino acid release from the skeletal muscle compartment resulting (ultimately) in net muscle protein breakdown. Indirect support for this hypothesis is given by two studies that demonstrated a specific association between muscle wasting and markers of systemic inflammation in COPD (46), as well as by another study linking hypermetabolism, increased levels of acute phase proteins and decreased plasma amino acid status (47). Skeletal muscle protein turnover has so far been investigated in only one study. Muscle protein synthesis rate was decreased in a group of underweight clinically stable patients with emphysema while protein breakdown rate was normal (48). Further research is needed to confirm or extend these findings.

3.2.2 Amino Acid Metabolism

Amino acids are the building blocks of protein and several studies have reported an abnormal plasma amino acid pattern in COPD. Of interest are the consistently reduced plasma levels of branched chain amino acids (BCAAs) in underweight COPD patients and in those with low muscle mass (49, 50). There are some indications that low plasma BCAAs in COPD patients are due to specific alterations in leucine metabolism, possibly mediated by altered insulin regulation and increased leucine oxidation in skeletal muscle to a non-

carbohydrate energy substrate (50). Leucine is an interesting nutritional substrate since it not only serves as a precursor, but also activates signalling pathways that enhance activity and synthesis of proteins involved in messenger ribonucleic acid (mRNA) translocation to upregulate protein synthesis in skeletal muscle (51).
In addition to fostering a higher rate of postprandial protein synthesis, increased availability of amino acids also enhances the stimulation of protein synthesis that occurs in response to exercise (52). The magnitude of stimulation however depends on the timing of amino acid administration relative to the period of exercise (52).

3.2.3 Inflammatory Modulation

Despite anabolic nutritional and/or pharmacological stimulation, (muscle) weight gain is limited in some COPD patients. As in other chronic inflammatory disorders, a poor therapeutic response is related to the presence of systemic inflammation (53).
The disproportionate muscle wasting, linked to systemic inflammation and unresponsive to nutritional supplementation, is commonly referred to as the cachexia syndrome (54). Current insight into the molecular mechanisms of cachexia indicates a complex interaction between inflammatory mediators, oxidative stress and growth factors, which are not only involved in an imbalance between muscle protein synthesis and breakdown, but also in processes that govern the maintenance of skeletal muscle and muscle plasticity such as skeletal muscle fibre degeneration, apoptosis and regeneration (54).
The fatty acid composition of inflammatory and immune cells is sensitive to changes in the fatty acid composition of the diet. The n-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid are found in high proportions in oily fish and fish oils. The n-3 PUFA are structurally and functionally distinct from the n-6 PUFA. Typically human inflammatory cells contain high proportions of the n-6 PUFA, arachidonic acid and low proportions of n-3 PUFA. The significance of this difference is that arachidonic acid is the precursor of 2-series prostaglandins and 4-series leukotrienes, which are highly active mediators of inflammation. Feeding fish oil results in partial replacement of arachidonic acid in inflammatory cell membranes by EPA. This change leads to decreased production of arachidonic acid-derived mediators. This response alone is a potentially beneficial anti-inflammatory effect of PUFA. Supplementation of the diet of healthy volunteers with fish oil-derived n-3 PUFA resulted in decreased monocyte and neutrophil chemotaxis and decreased production of pro-inflammatory cytokines (55). Clinical studies have reported that fish oil supplementation has beneficial effects on the systemic inflammatory response and disease activity in conditions such as rheumatoid arthritis and inflammatory bowel disease (55).
A Japanese study investigated the effects of a dietary supplement containing n-3 PUFA given for 2 years and reported a significant decrease in LTB4 levels in serum and sputum, and in tumour necrosis factor (TNF)-α and IL-8 in sputum, while no effect was observed in the control group receiving a nutritional supplement enriched with n-6 PUFA (56).
Positive effects of fatty acid modulation may also be related to other actions of n-3 PUFA which occur downstream of altered eicosanoid production or which may be independent of this activity. Nuclear factor kappa B (NF-κB) is a critical mediator of the intracellular signalling events triggered by TNF-α and other inflammatory cytokines, including skeletal

muscle specific gene expression. NF-κB activation has indeed been demonstrated in skeletal muscle of severely underweight patients with COPD (57). Recent studies have shown that n-3 PUFA can down-regulate the activity of NF-κB. The interaction of n-3 PUFA and cytokine biology is however complex. In healthy volunteers the sensitivity of a person to the suppressive effects of n-3 PUFA on TNF-α production is linked to the inherent level of production of the cytokines by cells from the person before supplementation and genetic variation encoded by, or associated with TNF-α–308 and lymph toxin +252 single nucleotide polymorphisms (58). Some studies suggest that TNF-α levels are particularly increased in COPD patients with weight loss and/or muscle wasting (46). TNF-α–308 polymorphism however has also been associated with the presence of COPD (59) and even specifically with the extent of emphysematous changes in these patients (60).

3.3. Muscle Oxidative Phenotype and Cellular Cnergy Metabolism

3.3.1 Cellular Energy Metabolism

Intrinsic abnormalities in peripheral skeletal muscle morphology and metabolism have been described in COPD patients, pointing towards decreased oxidative capacity. These abnormalities include muscle fibre type shifts from the oxidative type I fibres towards the glycolytic type IIx fibres (61), accompanied by a decrease in oxidative enzymes involved in carbohydrate and fatty acid oxidation (62). Detailed information about substrate metabolism and on whole-body and skeletal muscle levels in these diseases are lacking. Nevertheless, the metabolic adaptations have clinical consequence as illustrated for example by decreased mechanical efficiency (63) and enhanced lactic acid production during exercise (64) relative to healthy control subjects. In addition, NMR studies, using single limb exercise models, have shown a rapid decline and impaired recovery of phosphocreatine stores (65). Three studies have indicated that decreased oxidative capacity may be more pronounced in patients with emphysema, possibly related to altered O_2 availability (61, 66, 67).
Positive effects of pulmonary rehabilitation, in particular of endurance exercise training, illustrate that decreased muscle oxidative capacity in COPD is at least partly reversible (68), although detailed information on the effect of endurance training on substrate metabolism in COPD is lacking. While overall effects of endurance type exercise are positive, the available studies show that it is difficult to enhance this response by modulating exercise type and intensity alone (68,69). It is therefore tempting to explore the potential of nutritional modulation on muscle substrate metabolism to enhance improvement of exercise capacity in COPD.

3.3.2 Inflammatory Modulation

The muscle fibre type shift from type I to type IIx together with the enhanced lactic acid production during exercise points towards a decreased oxidative capacity specifically for fatty acids. This suggestion is consistent with the finding that 3-hydroxyacyl-coenzyme A dehydrogenase ((HADH) an enzyme involved in the ß-oxidation of fatty acids) is decreased in COPD (62), whereas cytochrome C oxidase (an enzyme of the respiratory chain) as well as phosphofructokinase (a glycolytic enzyme) were found to be increased in some studies

(70, 71). These disturbances can be located at the levels of cellular fatty acid uptake, mitochondrial fatty acid uptake and/or fatty acid oxidation. In the past decade, the peroxisome proliferator-activated receptors (PPARs) have emerged as positive regulators of skeletal muscle oxidative phenotype (72, 73). There are three PPAR isotypes, PPAR-α, PPAR-δ and PPAR-γ with the latter having a very low expression in skeletal muscle and being implicated in storage of fatty acids. The PPAR-α and PPAR-δ isotypes on the other hand are highly expressed in skeletal muscle and play a role in the transcriptional control of genes encoding mitochondrial fatty acid β-oxidation enzymes (72, 73). Many muscle genes that promote selective utilization of lipid substrates are up-regulated by *in vivo* administration of PPAR-α activators. Indeed, it has been shown that skeletal muscle PPAR-α protein content is increased by exercise training (74, 75). In addition, PPAR-α also regulates fatty acid utilization and expression of several genes involved in fatty acid β-oxidation (76).
Interestingly, skeletal muscle also expresses high levels of PPAR-δ. Activation of the PPAR-δ subtype increases fatty acid β-oxidation as well as mRNA levels of several classical PPAR-α target genes in both rodent and human skeletal muscle cells, and it has been shown that PPAR-δ protein, like PPAR-α protein, is induced in skeletal muscle after exercise (77). These results indicate that, in addition to PPAR-α, PPAR-δ also plays an important role in mediating lipid-induced regulation of oxidative pathways in skeletal muscle. Two observations in patients with COPD indicate that PPARs may be an attractive therapeutic modality. A decreased expression of PPARδ protein expression and PPAR-α mRNA expression was observed in skeletal muscle biopsies of severe COPD patients (78). Moreover a randomized clinical trial in patients with COPD participating in a pulmonary rehabilitation programme showed that polyunsaturated fatty acids markedly enhanced exercise capacity compared to placebo (79). These positive effects could be explained by modulating effects on PPAR content and activity in skeletal muscle as PUFAs are natural ligands of the PPARs.

4. Disease Exacerbations as Therapeutic Window

Many COPD patients suffer from frequent exacerbations leading to disease deterioration when systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify, commonly causing hospitalizations (80) that are the main drivers of COPD related costs (81). Determinants of vulnerable patient phenotypes and pathophysiological mechanisms behind the clinical presentation are not well studied and remain largely unknown. A number of defence mechanisms are induced and serve primarily to ensure a swift response to resolve the acute situation, but few effective drugs and procedures are available (82) to counteract the deleterious mechanisms that remain chronically (over)activated. Once at this stage, patients enter a disability spiral with devastating implications for body composition, skeletal muscle function, physical performance, quality of life, and life expectancy.
Skeletal muscle is particularly prone to damage; atrophy and a decreased oxidative phenotype develop early and soon reach irreversible stages. A number of mechanisms are involved and most of them can interfere simultaneously with metabolic function, muscle mass, and performance. It is important to note the complexity and interrelation of regulatory processes involved which are induced by various triggers including Inflammation,

renin-angiotensin-aldosterone and sympathetic system activation (83). A most recent insight regarding molecular pathways indicates that during acute pulmonary inflammation, TNF-α induced NF-$\kappa\beta$ activation is required for the transition to systemic inflammation and muscle atrophy (84). Acute exacerbations and commonly administrated high dose glucocorticosteroids induce insulin resistance. Some nutritional interventions could have the potential to reverse inflammatory mechanisms that induce insulin resistance but this field is not yet explored in COPD.

COPD patients have higher energy needs due to increased resting metabolic rate and whole body protein turnover during exacerbations (85). The subjective perceptions driving food intake are modified (e.g. loss of appetite due to the illness) and patients may not be willing or find difficulties in adjusting their nutritional pattern during exacerbations (86). To investigate the potential for nutritional support during hospitalization for exacerbation of COPD, a double blind study randomized 56 nutritionally depleted patients to 125ml of energy and protein rich fluid thrice daily (2.38MJ/day) *vs* a matching non-caloric placebo (86). This intervention was feasible and increased daily energy (15%) and protein (38%) intake.

In addition to calories and proteins, a balanced daily diet should cover the daily requirements of micronutrients, vitamins and minerals. In chronic disease, various causes increase the daily needs and these patients, including those with COPD, frequently present with specific malnutritions or deficiencies. The literature on these issues is generally sparse, with some recent exceptions presented but not limited to this review. Research on vitamin D has moved our interest beyond calcium and bone homeostasis to enter the field of pulmonary function with inflammation as a linking element (41). According to a trial by Lehouck et al (87), 100,000 IU of vitamin D supplementation every 4 weeks for 1 year in 182 patients with moderate to very severe COPD and a history of recent exacerbations generally had no effect *vs* placebo on time-to-first exacerbation. However, careful subgroup analysis indicates potential benefit in patients with severe vitamin D deficiency (rate of exacerbation ratio 0.57, 95% confidence interval 0.33 to 0.98). Critically ill patients in need of mechanical ventilation have reduced serum levels of trace elements (selenium, manganese, zinc) and supplementation has the potential to shorten the time spent with mechanical ventilation support (88). Some confirmatory data for COPD exacerbated by upper respiratory tract infection were published recently. In a randomized, double-blind, placebo-controlled trial, supplementation with Echinacea purpurea along with zinc, selenium and ascorbic acid for 14 days, but not with Echinacea purpurea alone or with placebo, resulted in significantly less severe and shorter episodes of exacerbation (89). Importantly, intervention was safe and well tolerated, with sleep disorders occurring as the most frequent adverse events. The field of micronutrient supplements appears promising with significant potential for interventional trials.

Complementary to nutritional support are anabolic interventions. Anabolic steroids specifically induce gain in fat free mass, improve exercise capacity, and can restore a response to a rehabilitation programme blunted by low-dose oral steroids as maintenance therapy (90). Recent experimental evidence for synergistic effects of anabolic steroids and glucocorticoids on muscle recovery may be particularly relevant in the recovery phase from an acute exacerbation (91).

The most potent physiological anabolic trigger is physical training, in particular resistance exercise. During exacerbation, patients experience severely limited physical performance, mainly due to dyspnoea or infection. Thus, patients need to maintain a sufficient anabolic drive through adjunctive intervention, and data supporting feasibility and safety of rehabilitation during or immediately after hospitalization are emerging. In a randomized trial comparing low-, moderate/high and no exercise during acute exacerbation of COPD, adherence of 80% was demonstrated and exercise was considered safe and feasible (92). In one step further Babu et al (93) randomized 38 patients during an acute exacerbation of COPD to regular physical therapy (physiotherapy) or to regular plus on-call physical therapy. The addition of on-call sessions increased the 6-minute walk distance and improved peak expiratory flow. Feasibility, safety, and effects of resistance training were investigated in a randomized trial of 40 patients hospitalized for a COPD exacerbation (94). In addition to routine physiotherapy, the intervention group performed three sets of eight repetitions of quadriceps resistance exercise that improved muscle strength and 6-minute walk distance at discharge, and promoted enhanced anabolic status in skeletal muscle as demonstrated in biopsy samples. If patients are too ill to undertake physiotherapy or if this is beyond available resources, transcutaneous electrical muscle stimulation can be considered. Meglic et al (95) tested the feasibility of this method in 19 patients hospitalized due to an exacerbation of COPD, and demonstrated good tolerability, feasibility, and safety of an average of 15 sessions per patient. Such an intervention improved quadriceps strength, which correlated to stimulation intensity during 14 sessions, without any adverse events (96).

5. Summary

Weight loss and muscle wasting are common extra-pulmonary features in COPD. Weight loss is more prevalent in advanced stages of the disease and in the emphysematous subtype, while hidden loss of muscle mass is also prevalent in moderate disease. Both decreased dietary intake and increased energy expenditure may contribute to weight loss in COPD. The cause of muscle wasting is still unclear but clinically stable COPD patients are able to increase protein synthesis after physiological or pharmacological anabolic stimulation. Patients with advanced COPD are also characterized by a decreased muscle oxidative capacity that may be an additional target for nutritional modulation.

6. References

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