LEADING ARTICLE

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Reversal of Chronic Obstructive Pulmonary Disease-Associated Weight Loss

Are There Pharmacological Treatment Options?

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Abstract

Poor nutritional status is associated with an increased incidence of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). While a number of factors have been shown to produce tissue catabolism, no single mechanism has been clearly identified as a primary cause for weight loss in patients with severe COPD. Without a clear understanding of the aetiology of weight loss, therapeutic strategies to reverse this process have historically been unsuccessful. A review of recent studies allows consideration of a model of mechanisms of weight loss. This model includes multiple pathways that may be activated singly or simultaneously to cause loss of weight, specifically lean body mass. These include energy imbalances, elevated levels of cytokines, tissue hypoxia and the effects of cocorticosteroid therapy.

To date, interventional studies that have looked at newer pharmacotherapies such as growth hormone and anabolic steroids in patients with COPD who are losing weight have not demonstrated reversal of weight loss or improvement in nutritional status. Currently, early identification of patients at risk for weight loss and aggressive nutritional supplementation coupled with an exercise programme has demonstrated the greatest benefit. However, with increasing understanding of the mechanisms that may be implicated, new targets for therapies are being identified.

Of particular research interest are molecules such as leukotrienes, hormones, tumour necrosis factor-α and acute-phase proteins, which are noted to be elevated in some patients with COPD-associated weight loss. Currently, inhibitors to some of these inflammatory substances are used therapeutically in other chronic illnesses such as rheumatoid arthritis and cancer cachexia. Future research may investigate their usefulness in COPD and direct new therapies that target the processes contributing to weight loss in these patients.

1. Extent and Impact of the Problem

Weight loss in patients with chronic obstructive pulmonary disease (COPD) is a common phenomenon, occurring in approximately 35–60% of patients with moderate to severe COPD.[1-3] While mechanisms causing this weight loss are not completely understood, it is known that loss of weight in patients with COPD is associated with higher morbidity and mortality rates.[4]

Wilson et al.[2] noted that nutritional status based on bodyweight influenced mortality independent of forced expiratory volume in 1 second (FEV_1). Specifically, mortality increased as bodyweight decreased in three cohorts of patients with FEV_1 <35%, 35–47% and >47% of predicted values, respectively (see figure 1). This effect was more notable in the cohort with less severe airflow obstruction. More recently Landbo et al.[5] prospectively examined a large group of patients with COPD and reported low body mass index (BMI) as a predictor of poor prognosis, more marked in those with FEV_1 <50% of predicted.

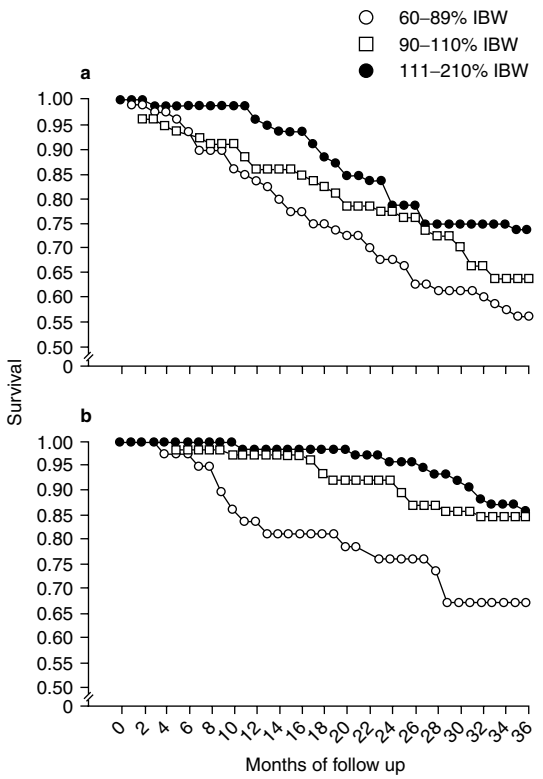

Fig. 1. Survival of patients with (**a**) forced expiratory volume in 1 second (FEV_1) 35% predicted by percentage of ideal bodyweight (IBW) category versus months of follow up and (**b**) FEV_1 35–47% predicted by percentage of IBW category versus months of follow up (reproduced from Wilson et al.,[2] with permission).

Recent findings indicate that weight loss and body composition abnormalities are independent predictors of morbidity and mortality in advanced COPD.[6] On the basis of these findings, screening for malnutrition in COPD patients should target vulnerable individuals earlier, prior to significant muscle wasting or weight loss, providing a window of opportunity for nutritional and pharmacotherapeutic intervention before body composition changes become irreversible.

COPD is the fourth most common cause of death in the US and results in direct medical costs of $US15 billion in the US alone.[7] Efforts to prevent the development of COPD target eliminating exposure to tobacco smoke and other lung irritants, while efforts to reduce severity of symptoms and slow progression of this disease process include smoking cessation, avoidance of infections, bronchodilators, anti-inflammatory medications, adequate diet and exercise, and oxygen in later stages. However, despite the best efforts towards this end, the disease progresses in some patients.

2. Effects of Weight Loss on Chronic Obstructive Pulmonary Disease (COPD)

Patients with COPD who experience weight loss usually have severe lung disease, with FEV_1 <25% predicted. However, depletion has been noted in patients with less severe disease, with FEV_1 between 45% and 55% predicted.[3] Nutritional depletion in COPD is an important determinant of both exercise and functional capacity.[3] Increased weight loss in patients with COPD is associated with increases in dyspnoea, fatigue, respiratory infections, decreased lung function, decreased peripheral muscle function and diminished respiratory muscle strength.[8-12] In addition, respiratory failure is more likely as weight loss progresses and results in

increased morbidity and mortality in this undernourished population.[2,13]

Reduced aerobic capacity has been demonstrated, with correlations between reduced percentage of ideal bodyweight (IBW) and lower indexes of maximal and submaximal aerobic capacity in patients with COPD.[14] These findings suggest that there is a negative effect of malnutrition on muscle aerobic metabolism. However, factors other than ventilatory limitation may impact on exercise performance. Alteration of peripheral blood flow may play a role, as could impaired energy metabolism. It has been suggested that the impairment or slowing of oxygen consumption (VO_2) kinetics may be related to an increased rate of anaerobic glycolysis with lactate formation. In addition, atrophy of type IIX muscle fibres has been demonstrated in the vastus lateralis in patients with COPD as compared with healthy control individuals.[15] In biopsy specimens from vastus lateralis muscles of patients with COPD, fibre cross-sectional area, and activities of cytochrome oxidase, succinate dehydrogenase and glycogen phosphorylase were lower than levels in healthy individuals. This is thought to be associated with a disturbed metabolic capacity related to loss of lean body mass.

It has been known for some time that patients with more severe COPD have a greater likelihood of poor nutritional status. Fiaccadori et al.,[16] evaluated the influence of severity of COPD on nutritional status.[16] A significant inverse correlation was noted between mean partial pressure of carbon dioxide in arterial blood (P_aCO_2) and percentage of IBW in three groups of patients with COPD of different degrees of severity. Those patients with both hypoxaemia and hypercapnia exhibited impairment of nutritional status that was proportional to the severity of illness. In addition, nutritional depletion was present in some of these patients in spite of apparent caloric intake in excess of basal energy expenditure. Newer findings have demonstrated that greater weight loss among COPD patients during hospitalisation and lower initial BMI on admission were significantly associated with unplanned early readmission.[17] This is further evidence of the relationship between nutritional status and morbidity in COPD.

3. Systemic Effects of COPD

Systemic manifestations of COPD include a number of extrapulmonary effects.[18] In addition to skeletal muscle dysfunction, osteoporosis is common in patients with COPD. While the use of both inhaled and oral corticosteroids may play a significant role in bone loss in patients with COPD, some studies have noted decreased bone density in COPD patients who had not received corticosteroids by any route.[19] In addition, sexual dysfunction has been described and linked to low testosterone levels in males with COPD.[20] To our knowledge, no controlled studies have specifically examined this phenomenon in the COPD patient population.

However, low testosterone levels have been documented in patients with COPD using systemic and inhaled corticosteroid therapy.[21,22] MacAdams et al.[21] examined the effect of long-term corticosteroid therapy on testosterone levels in patients with COPD. Compared with an age- and disease-matched group of control patients, those patients receiving long-term corticosteroid therapy for at least 1 month exhibited significantly lower testosterone levels. The corticosteroid dosage and serum testosterone level were inversely related in this group. This small study provides additional evidence that one possible mechanism causing low testosterone levels might be a corticosteroid-induced suppression of secretion of gonadotrophin-releasing hormone (GnRH) by the pituitary gland.

The effects of testosterone administration have been studied in several populations of men. Storer et al.[23] examined relationships between maximal voluntary strength, leg power, fatigability and testosterone dose in healthy, young eugonadal men in a double-blind, randomised study. Five separate groups of men were given monthly injections of long-acting GnRH agonist to suppress endogenous testosterone production, plus weekly injections of one of five testosterone doses for a period of 20 weeks. Leg muscle strength and leg power increased as testosterone dose levels increased across groups.

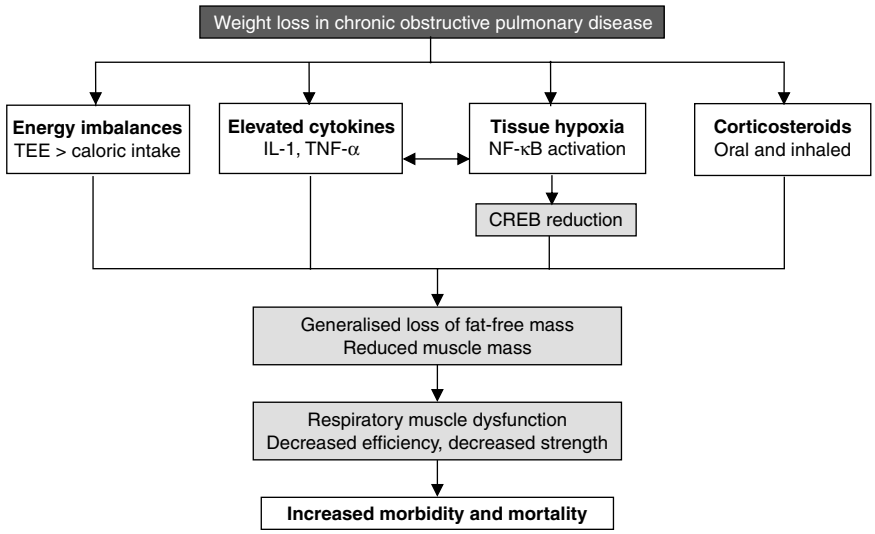

Fig. 2. Possible aetiologies for weight loss in patients with COPD. **CREB** = cyclic AMP response element-binding protein; **IL-1** = interleukin-1; **NF-κB** = nuclear factor-κB; **TEE** = total energy expenditure; **TNF-α** = tumour necrosis factor-α.

No relationship was noted between fatigability or specific tension and testosterone at any dose.

Testosterone replacement has been linked with deleterious adverse effects in a small sample of older men with hypogonadism.[24] Biweekly testosterone replacement for 12 months improved bilateral grip strength, haemoglobin level and lowered leptin levels. However, a significant dropout rate occurred because of the development of polycythaemia.

In summary, testosterone levels seem to be lowered by corticosteroid therapy and this may affect bone density, sexual functioning and other aspects contributing to quality of life. To date, beneficial effects on leg strength and power, grip strength and haemoglobin level have been demonstrated in specific age samples of men. Larger trials including frail, elderly patients are required to evaluate the benefits and risks of this therapy as well as the implications of improved grip strength to functional ability status and sexual dysfunction.

4. Possible Aetiologies for Weight Loss in COPD

Weight loss in patients with COPD may be a multifactorial phenomenon, resulting from a combination of various pathophysiological events. Abnormalities in energy balance, increased levels of cytokines, chronic hypoxia, exacerbations of COPD and corticosteroid intake can all influence food intake, substrate utilisation and metabolic efficiency (figure 2).[1,2,25]

4.1 Energy Balance

Loss of fat mass that is seen in undernourished patients results primarily from reduced caloric intake or increased energy expenditure. Pulmonary symptoms such as shortness of breath, copious secretions and cough can cause loss of appetite and energy for eating. Shortness of breath may increase during the effort of eating, making this an unpleasant task. It is difficult to swallow and breathe at the same time and the extremely dyspnoeic patient may be unable to coordinate breathing alternately with swallowing in an efficient manner. This will cause a diminished intake as the patient preferentially chooses to put energy and effort towards breathing.

In addition, both resting and total energy expenditure may be greater in patients with COPD. Resting energy expenditure (REE; the amount of calories burned [measured as VO_2] during rest) has been examined experimentally in patients with moderate

to severe COPD. In comparison with healthy age-matched individuals, elevated REE has been measured in 25% of COPD patients relative to fat-free mass.[25] In healthy controls, the amount of fat-free mass accounted for as much as 84% of the individual variation in REE in this study, whereas fat-free mass accounted for only 43% of individual variations in REE in patients with COPD. This suggests that other factors may also impact REE in COPD patients. In addition, Mannix et al.[26] noted that REE relative to lean body mass was greater in a group of malnourished COPD patients as compared with a group of normally nourished COPD patients and with a healthy control group. The malnourished patients also had lower FEV_1 and forced vital capacity values, higher carbon dioxide partial pressure values and lower arterial pH values. Thus, some studies have measured hypermetabolism among malnourished COPD patients. It is postulated that this may be largely because of an elevated 'cost of breathing' in these patients. In addition, total energy expenditure is also elevated, with even greater 'cost of breathing' induced during periods of activity.[27]

However, Sridhar et al.[28] found no evidence to indicate that the 'oxygen cost of breathing' and elevations in REE in patients with respiratory diseases including COPD are causally related to elevated weight loss. In this study, the 'oxygen cost of breathing' was elevated in all patients with a variety of respiratory diseases but none of the patients were below 90% of IBW.

4.2 Cytokines

Cytokine production and release during smoking and frequent infections may contribute to the anorexia and weight loss in patients with COPD. The cytokine profile in COPD patients is unique and unlike that seen in asthma patients. It is thought that increased levels of tumour necrosis factor (TNF)-α, and interleukin (IL)-1 and IL-8 may induce a catabolic response in tissues, triggering muscle proteolysis, with a resulting increase in protein degradation. Normally, this process is tightly regulated and must be balanced with protein synthesis; however, activation of the ubiquitin-proteasome pathway results in ongoing protein catabolism.[29] This specific response results from a series of adaptations that seem to enhance the efficiency of this pathway and promote muscle wasting during times of stress and tissue insult.

Multiple molecules including leukotrienes, hormones, TNFα, acute-phase proteins, C-reactive protein and lipopolysaccharide (LPS)-binding protein have been associated with increases in REE and weight loss in patients with COPD. However, elevated TNFα levels have been most clearly linked with weight loss in hypoxic patients with COPD-associated weight loss.[30,31] A recent study noted that oxygen delivery to the tissues was lower in weight-losing patients with increased TNFα levels,[31] although these relationships were not statistically significant in a small sample of 16 patients. TNFα is intermittently produced, with a half-life of 6–7 minutes, and seems to be activated by a number of mechanisms that include hypoxia. Thus, one discrete measurement may not be an accurate indicator of tissue production.[31] However, these findings suggest that serum TNFα production may be stimulated by tissue hypoxia and TNFα may be a factor contributing to weight loss in these patients.

4.3 Hypoxia

Chronic hypoxia, as a stimulus to cytokine production, increases the release of IL-1B and TNFα in human alveolar macrophages. The previously cited study[31] examining serum TNFα levels suggests that tissue hypoxia induces local expression of these cytokines in stable malnourished COPD patients. In addition, inverse correlations between soluble TNF receptor levels and percentage fat have been noted in COPD patients.[32] While the genes controlling TNFα and IL-1 are regulated by low oxygen tension, the transcriptional level may be altered by hypoxia through different mechanisms that are under study.[33] Hempel et al.[34] demonstrated that hypoxia, through decreased transcription of human prostaglandin (PG) H synthase-2 gene during exposure to LPS, causes a decreased level of PGE_2. As PGE_2 has been shown to inhibit IL-1 and TNF, these researchers further noted that subsequent to its ef-

fects on PGE_2, hypoxia increases the LPS-stimulated release of IL-1 and TNFα from the human alveolar macrophage.[35] Madjdpour et al.[36] and others[37,38] measured increased nuclear factor (NF)-κB binding activity and messenger RNA for TNFα, as well as other inflammatory proteins in rat and other mammal lungs in the presence of hypoxia. Currently, the mechanisms involved are under study. However, there is evidence that hypoxia may induce TNFα expression via induction of the NF-κB pathway in the rat model as well as mammalian cell cultures.[37,38] However, as cyclic adenosine monophosphate response elements (CRE) bind the CRE-binding protein (CREB) which inhibits TNFα expression, it has also been noted that hypoxia diminishes CREB expression in human intestinal cells.[39] Thus, at least two pathways have been identified that may separately or synergistically link hypoxia with increases in expression of TNFα. These findings provide supportive evidence that hypoxia activates the TNFα system, which then contributes to the cachexia observed in severe states of COPD. *In vitro* studies have demonstrated increases in TNFα in human monocyte cells of patients with COPD-associated weight loss incubated in hypoxic conditions.[40]

Chronic hypoxia is also thought to reduce serum insulin-like growth factor (IGF)-1 levels and cause growth impairment and tissue catabolism in hypoxaemic patients.[41] In a recent study, IGF-1 injections significantly increased weight in rats, especially during chronic hypoxic exposure, as compared with vehicle-treated rats. Also, IGF-1 treatment increased the serum total protein and albumin when hypoxic exposure was terminated. However, similar weight gain was noted between IGF-1- and vehicle-treated normoxic rats.[41]

The apparent paradox which classically describes patients with emphysema ('pink puffers': weight-losing) and patients with chronic bronchitis ('blue bloaters': normal or overweight) are questioned today. In a recent study, patients were grouped by these descriptions and measurements of lung function, arterial blood gases, TNFα, oxygen delivery and oxygen extraction ratio were obtained after right heart catheterisation.[31] 'Pink puffer' patients exhibited lower carbon monoxide diffusion in the lungs and higher total lung capacity, functional residual lung capacity and partial pressure of oxygen in arterial blood than 'blue bloaters'. In addition, oxygen delivery and tissue oxygenation were lower in the 'pink puffer' patients than in the 'blue bloater' patients. As weight loss is more evident in patients with emphysema than chronic bronchitis, it is suggested that emphysema patients have significant tissue hypoxia, which could be related to weight loss. However, patients with chronic bronchitis have well preserved tissue oxygenation, thought to be because of increased cardiac output and preserved oxygen content. Thus, these patients may not experience weight loss.[31]

4.4 Corticosteroids

Lastly, long-term corticosteroid use is associated with muscle weakness and loss of muscle mass in COPD patients as compared with matched COPD patients not taking corticosteroids.[42] In the rat model, corticosteroids stimulate proteolysis and inhibit both protein synthesis and transport of amino acids into the muscle cells. Corticosteroids and acidosis may activate the ubiquitin pathway that is known to increase protein degradation.[43] As corticosteroid use increases during exacerbations, there are several possible mechanisms concurrently contributing to the stimulation of this pathway. The net effect of these mechanisms is further loss of lean muscle mass.

5. Pharmacological Approaches to COPD-Associated Weight Loss

Patients with chronic inflammatory diseases such as COPD have been found to have alterations in several hormone systems involved in protein turnover. Insulin, growth hormone, IGFs and anabolic hormones enhance protein anabolism. In catabolic inflammatory conditions, fasting and anorexia, growth hormone levels may be normal or elevated; however, growth hormone receptor binding is reduced leading to reduced levels of IGFs.[44] In animals, infusion of IL-1 and TNFα results in reduced

levels of IGFs and suggests that there is a direct link between the release of cytokines and the regulation of the growth hormone axis.[45] Moreover, the effect of TNFα appears to be dose dependent and proximal to IGF-1 action on protein synthesis.[46] The reason for this cytokine-growth hormone pathway is unclear, although catabolism-associated reduction in IGF levels may in part reflect the need to limit the flow of substrate for muscle protein anabolism at a time when it is needed for the synthesis of anti-inflammatory mediators. The possibility also exists that the fall in IGF levels may represent a maladaptive response.

5.1 Growth Hormone

The advent of somatropin (recombinant human growth hormone; rhGH) has lead to a number of studies of its anabolic potential. Human studies of somatropin administration have demonstrated improvements in nitrogen balance consistent with the anabolic effects of this hormone.[47,48] Human growth hormone administration also counters the catabolic adverse effects of prednisone, making it a potentially useful medication for patients with COPD-associated weight loss.[49]

To date, small-scale, non-placebo-controlled studies of somatropin administration in COPD patients have provided conflicting results.[50,51] Burdet et al.[52] most carefully studied the effects of somatropin administration in a small sample of COPD patients in a placebo-controlled study that included exercise training and recommendations to increase daily caloric intake. Daily subcutaneous somatropin treatment for 21 days successfully raised circulating IGF-1 levels and although there was no significant difference in bodyweight (both groups gained ~2kg) there was a significantly greater increase in lean body mass in the somatropin-treated group compared with the placebo group (2.3 vs 1.1kg at day 21 and 1.9 vs 0.7kg at day 81, respectively). These results persisted despite cessation of treatment with somatropin at day 21. However, somatropin treatment had no effect on pulmonary function tests or functional parameters, indicating that any potential benefit in body composition was cosmetic at best.

In general, when assessing the results of anabolic hormone studies it is important to pay close attention to the methods used to measure body composition changes. In the study by Burdet et al.[52] body composition was assessed by dual-energy x-ray absorptiometry (DEXA). This technique uses low-level x-ray to discriminate between tissue densities. Unfortunately, the accuracy of DEXA is hampered by changes in salt and water balance. Fluid retention leads to an overestimation of lean body mass because of the predominance of water in lean tissue. Somatropin administration is known to cause salt and water retention, and this may have influenced the measurement of lean body mass by DEXA in the treatment group. However, there was no evidence of fluid retention in patients in the treatment group and lean body mass differences between treatment and control patients persisted for 2 months after end of treatment.

To summarise, growth hormone studies have not shown a clear clinical benefit for COPD patients, other than slight increases in lean body mass.

5.2 Anabolic Steroids

Investigators have examined the effect of anabolic steroids on body composition and functional status. In a placebo-controlled, randomised study of 217 patients with moderate to severe COPD comparing the physiological effects of nutritional intervention alone or combined with 8 weeks of intramuscular injections of nandrolone decanoate, Schols et al.[53] observed identical weight gains of 2.6kg in both groups. However, there was a disproportionately greater increase of lean body mass in the nandrolone decanoate-treated group. There were no differences in functional status; however, nandrolone decanoate treatment did result in a significantly greater maximal inspiratory mouth pressure after 8 weeks of treatment. Despite the fact that nandrolone decanoate treatment is relatively well tolerated, it requires intramuscular administration and lacks a US FDA indication for weight gain, which has led to consideration of alternative anabolic agents.

As with DEXA, bioelectrical impedance analysis (BIA) has general limitations in validity. BIA is a measure of impedance to conduction of electrical current through the body tissues and reflects water content of the body tissues. Conduction is enhanced by water content of tissue that is higher in lean tissue than in fatty tissue. Thus, patients who retain fluids will appear leaner than patients who are normally hydrated or dehydrated. In the study by Schols et al.,[53] additional body composition techniques were utilised including deuterium dilution and creatinine height index for muscle mass. Thus, cross validation of techniques was utilised to ensure the accuracy of the body composition changes recorded.[53]

Stanozolol, an oral anabolic agent, was examined in combination with exercise during a 6-month trial for its effects on lean body mass, BMI, respiratory muscle strength and functional exercise capacity in patients with COPD.[54] Seventeen male patients completed the study (treatment group, n = 10; control group, n = 7). All patients had moderate to severe airway obstruction. The mean BMI for the entire sample was 17, which is below the predicted for age and sex of this group. The treatment group was given an initial dose of testosterone intramuscularly followed by oral stanozolol 12 mg/day for 27 weeks, while the control group received placebo. Both groups participated in inspiratory muscle exercises for 18 weeks and cycle ergometer exercises for 9 weeks. At the end of 27 weeks, the treatment group displayed a mean (± SD) weight gain of 1.8 (± 0.5)kg while the control group lost weight. In the treatment group, lean body mass (as measured by DEXA) increased significantly from baseline while control patients showed no increase. The study group sustained the increase at 18 weeks. Both groups increased their inspiratory muscle strength, but the increases were not significant and nor were there differences between the groups. No change in functional exercise capacity was noted in either group.

Another oral anabolic agent, oxandrolone, has been US FDA approved as an adjunctive weight gain agent for use in patients with weight loss from chronic infection, severe trauma or extensive surgery. The ratio of anabolic to androgenic activity is high compared with methyltestosterone, making it a safely used alternative for male and female patients.

Yeh et al.[55] examined the anabolic effects of oxandrolone in COPD patients using a prospective open-label study without a control group. In this study, patients were followed for 4 months while taking daily oxandrolone without supplemental nutrition or exercise counselling. BIA was used to assess body composition, and other outcomes included pulmonary and functional status. By 2 months the average weight gain had plateaued at 2.3 ± 2.3kg, and declined slightly to 2.1 ± 2.7kg at 4 months. There was a preferential increase in lean body mass (body cell mass) over fat mass; however, there was no effect on spirometry results, or functional status as measured by the distance walked in 6 minutes. Karnofsky performance status scores improved marginally; however, in the absence of blinding these results are subject to bias.

The most striking aspect of this study was the large number of patients that withdrew or were removed because of adverse events. 128 patients were enrolled in the study but only 49 completed the study (34 dropped out because of adverse events, 28 requested to be removed, and 17 for miscellaneous reasons). The most common adverse events noted were oedema (17%), increased transaminases (12%), androgenic adverse effects (12%), nausea (9%) and alopecia (9%). These adverse effects are well recognised, but prolonged use raises the possibility of additional adverse effects such as bile retention and alterations in high-density lipoprotein and glucose metabolism. There is no conclusive evidence linking oxandrolone to malignancy but there have been claims that anabolic steroids may stimulate the growth of breast and prostatic cancers.[56]

In summary, studies with anabolic steroids have shown small benefits in lean body mass but no clear improvement in functional or pulmonary status. Larger placebo-controlled studies of anabolic steroids as an adjunct to nutrition support and exercise training are needed to further explore benefits of this treatment modality.

5.3 Megestrol

Treatment with megestrol, a progestational appetite stimulant, was examined in a recent study of underweight patients with COPD.[57] In a randomised, double-blind, placebo-controlled study, patients took either megestrol 800 mg/day or placebo daily for 8 weeks. Baseline measurements included height, weight, spirometry, maximum inspiratory pressure, maximum expiratory pressure, body composition with anthropometry and DEXA, arterial blood gas analysis, 6-minute walk and questionnaires, and acute-phase proteins. Additional similar measurements were done at weeks 2, 4 and 8. While there were no significant differences between groups at baseline, the megestrol-treated group gained significantly more weight than the placebo group (1.2 ± 1.4kg vs 0.6 ± 1.1kg). Most of the weight gain was determined to be fat mass, with an increase of 42% in the megestrol group compared with 0.1% in the placebo group. Other parameters were not significantly different except for the oxygen partial pressure (pO_2) and P_aCO_2, which increased and decreased, respectively, in the megestrol group. It appears that administration of megestrol for a period of 8 weeks increases appetite and bodyweight, and stimulates ventilation in COPD patients, with no serious adverse consequences.

5.4 Anti-inflammatories

Corticosteroids have been used in an attempt to lower airway inflammation, but studies have shown that the inflammatory response in COPD is essentially corticosteroid resistant.[58] Therefore, alternative treatments that attack the proximal mediators of the catabolic and inflammatory reaction are needed. For instance, studies directed at other mediators of weight loss and muscle protein degradation, and single-agent treatment or combination therapy with anabolic agents may prove to be most beneficial. Inhibition of TNFα (with antibodies or soluble receptors) and IL-8 activity (through the use of specific proteases or IL-10) may have beneficial effects both in terms of controlling disease activity and reversing effects on protein degradation.[59] IL-10 is an anti-inflammatory cytokine with wide effects. It inhibits the secretion of TNFα and IL-8 from macrophages. It also decreases the expression of matrix metalloproteinases as well as increases the expression of endogenous tissue inhibitors of matrix metalloproteinases. Currently in clinical trials for other chronic inflammatory diseases, it may also have therapeutic potential in COPD.[59]

5.5 Nutritional Invervention

Two additional studies warrant mention in that they both tested nutritional intervention and found improvement in important measures in patients with COPD. Marchesani et al.[60] administered oral organic phosphate in 45 malnourished, stable patients with COPD. All patients demonstrated improvement in maximal inspiratory pressures and a trend to improvement in visual analogue scale measures of dyspnoea and maximal voluntary ventilation compared with a control group of COPD patients not receiving oral organic phosphate – the control group received intravenous dextrose.

Creutzberg et al.[61] tested the effects of two to three daily oral liquid nutritional supplements incorporated into the regular diet of weight-losing COPD patients enrolled in an 8-week inpatient pulmonary rehabilitation programme.[61] Increases in bodyweight, fat-free mass as measured by BIA analysis, maximal inspiratory pressure, handgrip strength and peak workload on a stationary bicycle improved significantly as compared with an 'historical' placebo group taken from a prior study by one of the same investigators. In addition, disease-specific health status as measured by the St George's Respiratory Questionnaire also improved.

It has been noted for some time that polyunsaturated fatty acids may be biologically useful in the treatment of COPD. The consumption of diets high in fish oils in certain populations has been associated with a low prevalence of inflammatory lung disease.[62] The presence of omega-3 fatty acids displaces inflammatory precursors such as arachidonic acid from cell membrane lipids and lowers the production of inflammatory eicosanoids. Similarly, leukotrienes that are derived from arachidonic acid that act as proinflammatory mediators and stimulate

Table I. Potential therapies for reversal of weight loss in patients with chronic obstructive pulmonary disease

Therapy	Examples
Chemokine inhibitors	IL-8 antagonists: SB-225002 (selective CXCR2 antagonist that inhibits human neutrophil chemotaxis), SB-265610, monoclonal antibodies (ABX-IL-8)
Tumour necrosis factor-α inhibitors	Infliximab, etanercept, small molecule inhibitors
Anti-inflammatory agents	Phosphodiesterase-4 inhibitors, nuclear factor (NF)-κB inhibitors, adhesion molecule inhibitors, IL-10 and analogues, p38 MAP kinase inhibitors, PI-3 kinase-Y inhibitors, fish oils
Growth hormone	Somatropin (recombinant human growth hormone)
Anabolic steroids	Nandrolone decanoate, stanozolol, oxandrolone
Appetite stimulants	Megestrol
Supplemental nutrition and exercise	

CXCR2 = CX chemokin receptor 2 (or IL-8RB); **IL** = interleukin; **MAP** = mitogen-activated protein; **PI-3** = phosphatidylinositol-3.

bronchoconstriction are reduced as a response to fish oil supplementation. Further support for the possible benefits of fish oils is provided in the study by Pacht et al.,[63] which reports the anti-inflammatory effects of eicosapentaenoic acid (EPA) and γ-linolenic acid (GLA) in enteral nutrition in patients with acute respiratory distress syndrome. In this prospective, randomised, double-blind, controlled clinical trial, patients receiving EPA and GLA showed a decrease in IL-8 and leukotriene B_4 as well as neutrophils and alveolar membrane protein permeability. However, there are no published studies which examine the role of fish oil in preventing weight loss in patients with COPD.

Finally, recent research has identified a novel tissue-specific protein that is secreted by adipose tissue.[64] This protein, adiponectin, is positively associated with insulin sensitivity in healthy human individuals and in diabetic patients, and is inversely related to the degree of adiposity. Evidence indicates that adiponectin has properties that are anti-atherogenic, anti-inflammatory and antihyperglycaemic. This protein suppresses cytokine production from macrophages and further investigation will determine if it has a future role as a therapeutic tool targeting inflammation.

6. Conclusion

Clearly, the complex mechanisms related to weight loss in COPD have not yet been fully described. Reversal of weight loss in this patient population by pharmacotherapy has not been clearly demonstrated as a 'safe', effective therapeutic option. While likely targets for therapy have been identified, additional controlled studies must be conducted to test new agents and clearly identify long-term effects. Table I summarises current and prospective therapies under study. Presently, early identification of patients with COPD who are at risk for undernutrition, smoking cessation, aggressive nutritional supplementation, exercise programmes and oxygen therapy will prolong functional ability and provide additional time as research on this topic advances.

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