

**REVIEW**

## Weight loss in chronic obstructive pulmonary disease

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**ABSTRACT:** Weight loss occurs in about a third or more disabled patients with chronic obstructive pulmonary disease (COPD), and appears to be a poor prognostic factor. As such, it correlates only weakly with FEV<sub>1</sub>, transfer factor and other measures of respiratory physiology and is probably, to a certain extent, independent of them. Recent studies of basal metabolic rate (BMR) in COPD using steady-state, non-invasive calorimetry, have shown it to be elevated by 10-20% in up to 40% of such patients. It is likely that this represents true hypermetabolism per kilogram of fat free mass. An elevated BMR cannot be predicted from combinations of detailed lung function tests or arterial gases, as patients with similar physiology have differing BMRs. Thus, although an increased work of breathing is the probable explanation for some of the increase, other factors such as cytokines or possibly drug therapy almost certainly contribute.

Muscle loss in weight-losing COPD appears to involve both type I and type II fibres, because of a combination of reduced calorie intake and disuse atrophy. Respiratory muscles share this fibre loss. Review of the controlled studies on nutritional supplementation in COPD suggests that an energy increase of about 30% is needed to achieve substantial weight gain and improve exercise tolerance. Fat-rich supplements have some theoretical advantages. Further work is needed particularly with regard to the determinants of the increased BMR in COPD, and the effect of longer term nutritional supplements on prognosis.

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Severe chronic obstructive pulmonary disease (COPD) is frequently marked by weight loss [1-6]. Although the mechanism is not fully understood, it is of clinical importance, since patients who are losing weight have a poorer prognosis than those who are of stable weight [1, 4], and there is some evidence that it may be a prognostic factor independent of, or at least not closely correlated with, the degree of airflow obstruction [7].

### Weight loss in COPD

In COPD, low body weight is strongly correlated with worse disease state, and may be found in more than a third of more disabled patients [2, 5, 7-10]. In the 779 COPD patients studied in the US Intermittent Positive Pressure Breathing (IPPB) Trial, 95 out of 275 (35%) with forced expiratory volume in one second (FEV<sub>1</sub>) less than 35% predicted, were less than 90% ideal body weight (IBW), compared with 54 out of 262 (21%) with an FEV<sub>1</sub> between 35-47% predicted, and 38 out of 242 (16%) with an FEV<sub>1</sub> between 47-60% predicted [7]. Similarly, in a study of 153 COPD patients, with a mean FEV<sub>1</sub> of 38% predicted, SCHOLS *et al.* [10] showed that 30 hypoxic patients (mean arterial oxygen tension (Pao<sub>2</sub>) 6.5±0.7 kPa) were significantly lighter than 123 patients with mean Pao<sub>2</sub> 10.1±1.7 kPa. A similar positive

correlation was seen for the transfer factor, and an inverse correlation for total lung capacity (TLC). Although loss of weight is sometimes taken to be a "terminal" event in the progression of COPD [1], there is now evidence that, independently of FEV<sub>1</sub>, it is a poor prognostic factor for survival even in patients with an FEV<sub>1</sub> greater than 40% predicted [7].

### Mechanism of weight loss

#### Intake

Weight loss occurs when energy expenditure exceeds energy intake, *i.e.* when an individual is in negative energy balance. Although patients may lose weight acutely in exacerbations of COPD, they usually regain it upon recovery. In the majority of patients, weight loss appears to develop gradually, when they are otherwise in a stable clinical state [8, 9].

Two early studies of dietary histories in COPD patients [1, 2], showed that their calorie intake was equivalent to, or exceeded, their estimated daily requirements. However, intake estimates from dietary studies are not very reliable, and it has more recently been shown that the energy requirements of some COPD patients who are losing weight may be abnormally high [11].

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In healthy man, the normal adaptation to an increase in energy requirements, is a *pari passu* increase in calorie intake.

The reasons for a relatively deficient energy intake in COPD are not clearly understood. It has been suggested that patients with severe COPD may eat suboptimally because chewing and swallowing may change breathing pattern and decrease arterial oxygen saturation ( $Sa_{O_2}$ ) [12, 13]. Furthermore, gastric filling in these patients may reduce the functional residual capacity (FRC) and lead to an increase in dyspnoea [13]. It is possible that the hypothalamic appetite regulator is abnormal in COPD, but no evidence for this hypothesis is available.

Thus, the energy requirements of some of these more breathless patients are likely to be greater than predicted from standard tables, and attempts to increase oral intake may be difficult for mechanical reasons.

### Energy expenditure

There have now been many studies of metabolic energy expenditure in COPD, using non-invasive calorimetric methods in the stable state [5, 14–18]. In sedentary patients, the major component of 24 h energy expenditure is the resting energy expenditure (REE), with diet-induced thermogenesis (DIT) contributing approximately 15% to the total. Exercise-induced thermogenesis contributes a variable amount, but is almost certainly smaller in these less active patients. For example, DIT might typically be about  $375 \text{ cal-day}^{-1}$ , equivalent in energy expenditure terms to walking at  $5 \text{ kph}^{-1}$  for 1 h carrying a 20 kg load.

These recent metabolic studies have shown that many patients with COPD have basal rates of energy expenditure, some 10–20% higher than predicted from age, height, weight and gender using the Harris-Benedict equation. An elevation of energy expenditure of 10–20% above energy intake, would explain the weight loss. In the case of a patient who is expending about 500 kJ of energy above intake per day, a weight loss in the order of 10% of body weight over 1–2 yrs would be expected. The proportion of patients who are hypermetabolic has not been estimated in a large cohort, but was about 40% in smaller studies, where the mean  $FEV_1$  was about 1 litre [16, 19]. Hypermetabolism appears to be more common in more severe disease, and in patients who are losing weight [5].

However, the Harris-Benedict equation for predicted basal metabolic rate (BMR) in these studies assumes a standard body composition. A better way of expressing metabolic rate under these circumstances is as a function of fat free mass. However, to date, the use of skinfold anthropometry to derive this has not been validated in COPD, and it is possible that it is overestimated. Bioelectrical impedance (BI) measurements may be better, but the same criticisms apply. In 32 COPD patients, SCHOLS *et al.* [20] recently reported a very high (0.93) correlation between BI and total body water measurements made by deuterium dilution. However, this study did not allow the strict validation of BI as a measure of fat free mass (as opposed to total body water) in these subjects. More research in this area is required, but the

available evidence supports the conclusion that there is indeed hypermetabolism in COPD when BMR is expressed as a function of fat free mass.

The other difficulty here is that not all COPD patients who lose weight are hypermetabolic [21]. The increase in metabolic rate has been attributed to an increase in respiratory muscle work, since the energy cost of increasing ventilation is higher in patients with advanced COPD than in healthy controls of comparable age and gender [22]. However, REE correlates only weakly [5], or not at all [23], to individual or combinations of detailed lung function tests and blood gases, including measurements of volume and transfer factor. Thus, patients with the worst lung function, and in whom the work of breathing should be the highest, are not necessarily hypermetabolic. In addition, in a recent report, nasal intermittent positive pressure ventilation, which eliminated diaphragmatic and intercostal activity, did not reduce BMR to normal in a group of hypermetabolic patients [24].

Thus, whilst an increased work of breathing may contribute to weight loss, there is no convincing evidence that this is the only explanation, and other factors which could stimulate metabolism have to be considered. Possible candidates include catecholamines, cortisol and thyroid hormones, cytokines and drug treatment.

Circulating cortisol and thyroxine levels are normal in COPD [19]; noradrenaline but not adrenaline levels are raised [23]. It is not known whether the latter causes any change in skeletal muscle  $\beta$ -receptor density or sensitivity, and there have been no experiments directly to test the hypothesis that high catecholamine levels in COPD contribute to hypermetabolism. Likewise, it is not known whether the routine use of inhaled  $\beta$ -agonists increases metabolic rates. Even if it did, their use could only partly explain the raised BMR in COPD; whereas this may be increased by 10–20% above normal, two weeks of oral terbutaline sulphate increased BMR by less than 8% in healthy men [25]. Furthermore, in 23 patients with chronic asthma or tobacco-related COPD, there was no correlation between inhaled  $\beta$ -agonist dose or theophylline dose and BMR [23].

Another possibility is that hypermetabolism is cytokine-mediated. The polypeptide cytokine tumour necrosis factor (TNF) is produced by monocytes and macrophages. It inhibits lipoprotein lipase activity and is pyrogenic [26, 27]. It also triggers the release of other cytokines, including interleukins-1 and 2, which themselves mediate an increase in energy expenditure, as well as mobilization of amino acids and muscle protein catabolism [27, 28]. Cytokines are raised in cardiac cachexia [29], and they could be associated with the weight loss and hypermetabolism seen in COPD. Further work is needed to define their role.

### Skeletal muscle metabolism in COPD

Skeletal muscle is a major component of fat free body mass. Postmortem studies have shown a correlation between body weight and diaphragm muscle mass [30];



and that in emphysematous patients diaphragm weights were less than predicted from body weight [31]. Whether, in COPD, loss of respiratory muscle mass leads to physiologically important decreases in function is less clear. Experimental work in animals has shown that diaphragm weight and, therefore, maximal force was decreased in proportion to induced total body weight loss, as compared with normally nourished controls [32, 33]. However, this loss of muscle bulk was predominantly amongst the type II fast-twitch (mainly glycolytic-dependent) fibres, and less marked in the type I, or slow-twitch, oxidative, fibres. If this were to happen in COPD patients, then one might expect that maximum power output of the respiratory muscles would be decreased, whereas muscle function during basal activities would be less affected [34].

In underweight humans without lung disease, respiratory muscle power measured by maximal static inspiratory pressure ( $P_{I\max}$ ) and maximal static expiratory pressure ( $P_{E\max}$ ) is lower than in well-nourished controls [35, 36]. However, studies in COPD patients have produced conflicting results. Three have shown a reduction in  $P_{I\max}$  and  $P_{E\max}$  in lighter or malnourished patients [22, 37, 38], whilst three others could not demonstrate this [11, 39, 40]. A conclusion is, therefore, difficult, but it seems likely that a clinically important decrease in respiratory muscle strength is probably not present in all underweight patients with COPD, although it is probably the case in the most severely affected.

The factors likely to lead to a loss of muscle bulk in COPD have been considered above, but the interaction between the clinical and metabolic abnormalities in COPD and skeletal muscle function needs to be considered separately.

Skeletal muscle atrophy quickly follows disuse, and is commonly seen in bed-rested patients. Physical inactivity could contribute to muscle wasting in severe COPD. Since disuse-wasting, in contrast to malnourishment, mainly affects type I fibres, one would expect aerobic exercise performance, including respiratory muscular work, to be impaired more than anaerobic capacity, in relation to the degree of wasting. In particular, loss of oxidative capacity would be expected to reduce the aerobic, but not the anaerobic, regeneration of adenosine triphosphate (ATP) during muscular activity.

There are two anaerobic mechanisms for restoring ATP, one involving the breakdown of creatine phosphate to provide inorganic phosphate, and the other involving anaerobic glycolysis. Creatine phosphate stores are limited, being exhausted within 5–8 s of maximal exercise. These stores are subsequently replenished by the aerobic breakdown of ATP. Thus, if the ratio of inorganic phosphate to creatine phosphate is abnormally high, the aerobic capacity of the muscle must be reduced. The concomitant decrease in pH would be expected to interfere with the contractile mechanism, thereby contributing to fatigue. Evidence for such an explanation for impaired exercise performance in COPD comes from two recent studies of muscle metabolism, using nuclear magnetic resonance (NMR) spectroscopy, published in a former issue of this journal [41–43].

In the absence of infection or right ventricular failure, patients with stable COPD were found to have normal resting levels of forearm muscle intracellular substrates and pH. However, with increasing levels of forearm muscular work, these patients displayed an abnormal rise in the ratio of inorganic phosphate to creatinine phosphate, and an abnormal fall in pH. These results are consistent with the presence of impaired muscular oxidative capacity in COPD. Although this impairment is probably because of disuse-wasting of oxidative fibres (mainly type I) it could also be secondary to reduced tissue blood flow.

By contrast with the normal intracellular substrate and pH levels seen in stable COPD, biochemical studies have shown aberrations in skeletal muscle metabolite levels in patients during acute infective episodes [44, 45]. In particular, the quadriceps and intercostal intramuscular pH, and concentrations of ATP, creatine phosphate and glycogen were lower, and those of glucose and lactate were higher, on admission than at discharge [44]. The patients with the longest duration of an exacerbation before hospital admission had the lowest ATP levels. Reduced availability of energy-rich compounds for respiratory muscular work would be expected to reduce the efficiency of respiratory muscle activity. All of these patients received parenteral nutrition during part of their hospital stay, and at discharge the concentrations of intramuscular metabolites were much improved.

These results imply, that skeletal muscle function is abnormal in some COPD patients, and is likely to be worse in exacerbations. Extrapolation from these limb muscle studies to conclusions about respiratory muscle physiology must be made with care, however, because of the differing proportions of fibre types [46].

### Nutritional supplementation

To increase body weight in malnourished COPD patients, and thereby improve their muscle function, would seem to be a logical treatment in the light of the foregoing experimental evidence, but it has not yet been shown that this results in a better prognosis. The data available are essentially from short-term studies, with weight gain and some functional indices as end-points.

The first question is whether malnourished COPD patients handle nutrients normally, or whether, like septic patients, they are catabolic, and unable to improve nitrogen balance despite an increased protein intake. GOLDSTEIN *et al.* [14] showed that there appeared to be an increased utilization of carbohydrate in malnourished COPD patients, compared with malnourished patients without lung disease. However, two more recent studies have suggested that the metabolic response to food in COPD patients is in fact similar to healthy age-matched controls, with no consistent evidence for the preferential utilization of glucose, or differences in protein oxidation [16, 19]. Thus, it seems unlikely that fuel oxidation in stable COPD patients is abnormal; and weight gain should be expected as a result of increased mixed nutrient intake.



There have been five controlled studies of nutritional supplementation in COPD [39, 40, 47–49]. Patient numbers ranged 7–25, duration 8–13 weeks, and calorie intake 15–48%, above the control groups. Only the patients with energy increases of more than 30% appeared to increase body weight and to have improvements in respiratory muscle function or exercise performance. There is now an urgent need for more studies in this field, since this conclusion depends largely on the single study by EFTHIMIOU and co-workers [48].

High carbohydrate loads could theoretically be worse for COPD patients, because of their reduced capacity to excrete the resulting CO<sub>2</sub> load. This has been observed in ventilated patients receiving total parenteral nutrition (TPN) [50, 51]. However, in ambulant patients, these effects seem small [52, 53]. Nevertheless, there may be an advantage in prescribing high fat, rather than high carbohydrate supplements. EFTHIMIOU and co-workers [54] have recently studied ventilatory parameters, 6 min walk distance, and perceived breathlessness, in 10 COPD patients receiving double-blind, 920 kcal in a fat rich drink, or an isocaloric amount of a carbohydrate-rich drink, or an equal volume of a control liquid. They found that the carbohydrate-rich drink resulted in significantly greater increases in minute ventilation ( $\dot{V}_E$ ), carbon dioxide elimination ( $\dot{V}_{CO_2}$ ), oxygen consumption ( $\dot{V}_{O_2}$ ), respiratory quotient (RQ), arterial carbon dioxide tension (Paco<sub>2</sub>) and Borg score, together with a greater fall in the distance walked in 6 min, than the fat-rich drink. This result is similar to an earlier study by BROWN *et al.* [55]. Few data exist comparing different methods of supplementation in clinical practice, although experience suggests that supplements given between meals, and supplemental oxygen during feeding need to be considered [12, 56].

The interesting suggestion has been made in preliminary reports, that growth hormone therapy may improve nitrogen balance in COPD. This is likely to be due to increased insulin concentrations, since insulin promotes protein synthesis, whilst inhibiting protein degradation and urea synthesis [57, 58].

### Summary

Figure 1 shows a model of the events which may lead to weight loss in some patients with COPD. This hypothetical cycle starts with lung damage, leading to impaired lung function. This causes an increase in the energy cost of breathing, thereby increasing the body's total energy requirements. In the absence of a compensatory increase in energy intake, both fat and fat-free mass are lost. The loss of skeletal muscle mass impairs exercise performance, and the loss of respiratory muscle mass, in particular, causes further impairment of alveolar ventilation. As the disease progresses, the patient becomes more dyspnoeic on effort which, together with the decline in muscle mass, makes him more sedentary, thus causing further muscle wasting and a reduced capacity for protein synthesis. In addition, humoral factors may stimulate the metabolic rate and push the patient further into negative energy balance. The end result of such a cycle would eventually be dramatic weight loss. Many elements of this cycle require further research, which is important because of the independent adverse prognostic effect of weight loss in COPD.

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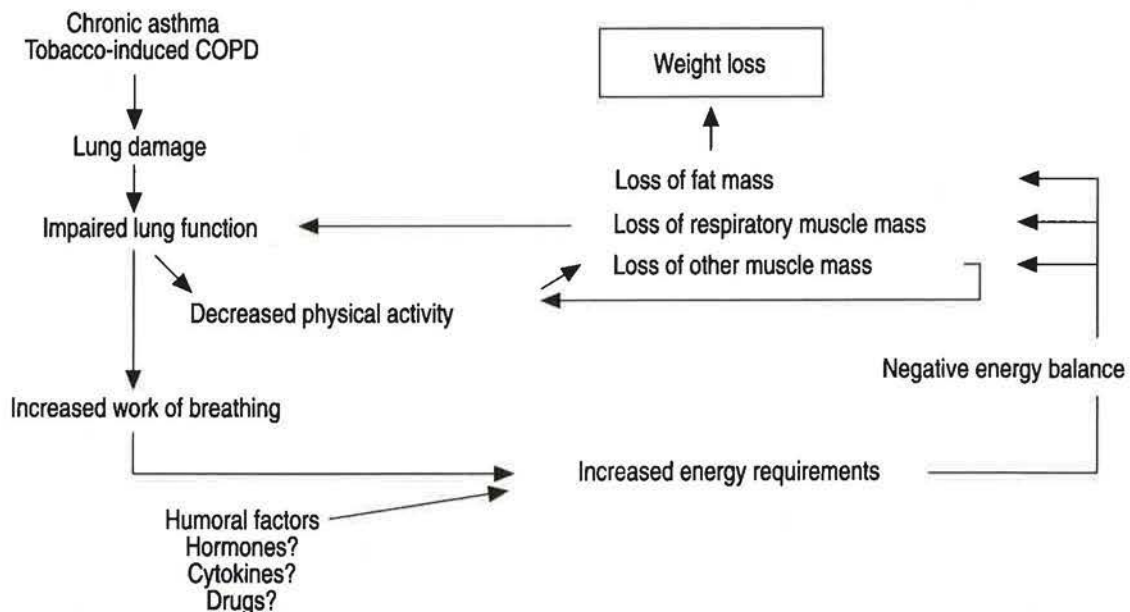


Fig. 1. – Hypothetical cycle of positive feedback leading to weight loss in chronic obstructive pulmonary disease (COPD).



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