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Systemic effects of COPD

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Summary Chronic obstructive pulmonary disease (COPD) is characterised by a range of pathological changes of the respiratory system, including airflow limitation secondary to structural changes of the small airways and loss of alveolar attachments, inflammation, ciliary dysfunction, and increased mucous production. COPD also has significant systemic consequences. The relationships between these pulmonary and nonpulmonary morbidities are not fully understood, and this further complicates the assessment of disease severity and prognosis. Although improving lung function and disease symptoms have been the main focus of COPD management, these parameters alone do not reflect the full burden of disease. More recent endeavours have highlighted the potential role of addressing physical limitations imposed by systemic alterations.

It is evident that systemic manifestations are common in COPD. Indeed, many patients demonstrate a gradual and significant weight loss that exacerbates the course and prognosis of disease. This weight loss is often accompanied by peripheral muscle dysfunction and weakness, which markedly contribute to exercise limitation and impaired quality of life. Weight loss has been postulated to be the result of a high metabolic rate that is not compensated for by increased dietary intake. The cause of this elevated metabolism is a matter of much debate, and several factors have been implicated. Similarly, the processes underlying depletion of muscle mass and function have not been fully delineated.

The impact of the systemic manifestations of COPD is substantial, and although many attempts have been made to elucidate the mechanisms underlying these manifestations, there are important questions, which remain to be answered. An

Abbreviations: BCM, body cellular mass; BIA, bioelectrical impedance analysis; COPD, chronic obstructive pulmonary disease; CXCL-8, CXC chemokine ligand-8; FEV_1, forced expiratory volume in 1 s; HRQoL, health-related quality of life; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LBM, lean body mass; OCB, oxygen cost of breathing; QF, quadriceps force; QoL, quality of life; 6MWD, 6-min walk distance; SGRQ, St. George's respiratory questionnaire; TNF-α, tumour necrosis factor-alpha

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increase in our understanding in this field will doubtless highlight potential therapeutic targets, and assist in guiding future therapeutic development.

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating multicomponent respiratory condition. The pathogenesis and clinical manifestations of COPD are not confined solely to pulmonary inflammation and structural remodelling, but extend to and encompass a variety of systemic alterations.[1] These extrapulmonary effects include systemic inflammation, nutritional abnormalities and weight loss, skeletal muscle dysfunction and additional organ effects. The high burden of COPD resulting from respiratory symptoms, such as breathlessness and exacerbations, is further contributed to by systemic effects, leading to a pronounced deterioration in health status and a diminished quality of life (QoL). Recently, there has been a much greater appreciation of the clinical importance of the systemic manifestations of COPD.[1] This article will focus primarily on the systemic nutritional and muscular components of COPD, discussing aetiology, diagnosis and treatment approaches.

Nutritional abnormalities in pulmonary disease: evidence from epidemiological studies

The most obvious clinical expression of nutritional abnormalities is unexplained weight loss.[1] Evidence of a relationship between body weight and COPD first emerged from a study investigating metabolic imbalances in severe bronchial obstruction.[2] The authors detected a meaningful correlation between low body weight and reduced survival rates in the participants, highlighting for the first time the role of nutritional depletion in COPD. This observation was later confirmed and extended, in a large population study, in which body weight was found to be directly related to severity of lung function determined by the forced expiratory volume in 1 s (FEV_1).[3] This study also provided additional information on the role of body weight on survival—mortality was found to increase as patient body weight decreased, regardless of lung function impairment. Low body weight therefore appears to be an independent marker of poor disease outcome.[4]

Aetiology of nutritional depletion: what, why and how?

Several studies have shown that malnutrition or reduced body weight is common in individuals with COPD, affecting approximately 10–15% of patients with mild-to-moderate disease, and 50% of patients with advanced-stage disease and chronic respiratory failure.[5–8] The pathophysiological basis of weight loss is not very well understood, although a high metabolic rate that is not compensated for by a corresponding increase in caloric intake is thought to play an important role.[9,10] The cause of the increased basal metabolic rate, however, is a matter of much debate and several hypotheses have been proposed (Fig. 1).

One hypothesis implicates increased energy expenditure, with the increased oxygen consumption by respiratory muscles that results from the increased workload required to overcome airway obstruction—the hallmark of COPD.[11] More recently, however, other studies have demonstrated that increased oxygen consumption is also evident in skeletal, non-respiratory muscle in COPD patients. Furthermore, breathing efficiency is comparable between patients with COPD, and healthy volunteers.[12] The role of the oxygen cost of breathing in the hypermetabolic state of COPD, therefore, remains uncertain.

Other factors implicated in raising basal metabolic rate include medications commonly used in the treatment of COPD (e.g. β_2-agonists and the phosphodiesterase inhibitor theophylline) and catecholamines (e.g. noradrenaline), although studies investigating the role of these hormones in hypermetabolism are limited. In addition, inflammatory mediators, such as tumour necrosis factor-alpha (TNF-α), C-reactive protein and lipopolysaccharide-binding protein are thought to play a role.[13] Finally, the increased thermic effect of patient activity has also been reported to contribute to the increased metabolism observed in COPD patients.[14]

Assessing nutritional status: methods of evaluation

Depletion in fat-free mass (including skeletal muscle) accounts for much of the observed weight loss in COPD, although cases have been reported in which alterations in body composition occurred even in the absence of any obvious weight loss.[8,15,16] Several methods are employed for measuring body composition. Anthropometry is a simple and widely used approach for assessing fat mass through skinfold thickness, body circumference, body mass

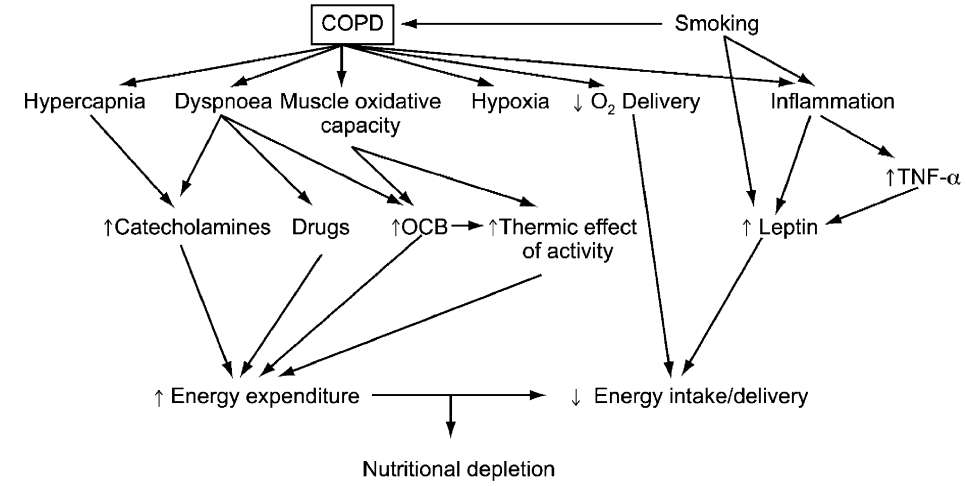

Figure 1 Pathogenesis of nutritional depletion in COPD: a multicomponent disease.

index and body weight parameters, although the assumption that the measured fat layer is representative of total body fat may lead to an underestimation or overestimation of fat mass.[14,17] More sophisticated methods are used to detect subtle changes in body composition. For example, dual-energy X-ray absorptiometry—where a double photon beam generated by an X-ray source is used to distinguish between different body tissues—is a reliable, non-invasive and easy to perform method. However, because of cost considerations and the need for normative reference data, this technology is not yet widely applied to determine nutritional depletion in COPD.[14,18] On the other hand, bioelectrical impedance analysis (BIA) is a simple, non-invasive and inexpensive tool for measuring nutritional status in COPD. By applying a low alternating current through electrodes attached to the wrist and ankle, the resulting resistance provides a good method for estimating lean body mass (LBM).[19] Compared with traditional anthropometric approaches, BIA provides a more accurate evaluation of nutritional abnormalities.[20]

Impact of nutritional depletion on COPD outcomes: a poor prognosis?

From a clinical viewpoint, the altered nutritional status associated with the progressive impairment of respiratory function in COPD poses a serious problem and its impact on the natural course of COPD is, therefore, of paramount importance.

To understand how nutritional depletion can influence disease outcomes, studies have examined the effect of reduced body weight on exercise tolerance,[17,21] QoL[7] and mortality.[3,4,6,22] A compromised nutritional state was shown to limit exercise performance in patients with COPD by reducing the aerobic capacity of exercising muscles.[17,21] Further evidence (Del Ponte et al., unpublished data) in support of this effect comes from reports of a strong correlation between 6-min walking distance, and the quantity of metabolically active lean body cellular mass (BCM; Fig. 2) in a group of 50 patients with stable COPD, presenting with FEV_1 40.66 ± 10.82 (mean ± SD). To assess the impact of reduced body weight on health status outcomes, one study has evaluated the relationship between nutritional status and health-related quality of life (HRQoL) using the St. George's Respiratory Questionnaire (SGRQ).[7] It was found that abnormally low body weight was associated with greater impairment in health status, reflected by low SGRQ scores. Moreover, increased dyspnoea was the most influential predictor of HRQoL, a respiratory symptom reported to be particularly prevalent in underweight patients.[7,23]

The impact of low body weight on patients with COPD was found to correlate with morbidity in relation to exacerbations in a group of 68 patients with severe, stable COPD (54 males) with chronic respiratory failure (mean ± SD PaO_2: 53.7 ± 6.00) kept on long-term oxygen therapy (Fig. 3; De Benedetto et al., unpublished data). This provided support to observations from an earlier study, in which malnutrition was reported to be associated with a poor outcome following an acute exacerbation in patients with respiratory failure.[24] The reduction in active cell mass in these individuals

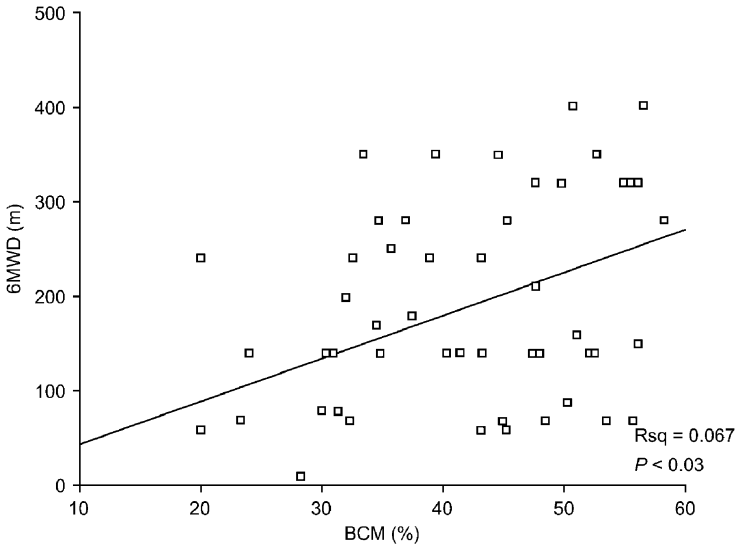

Figure 2 The relationship between body cell mass (BCM) and 6-min walk distance (6MWD) in patients with stable COPD (Del Ponte et al., unpublished data).

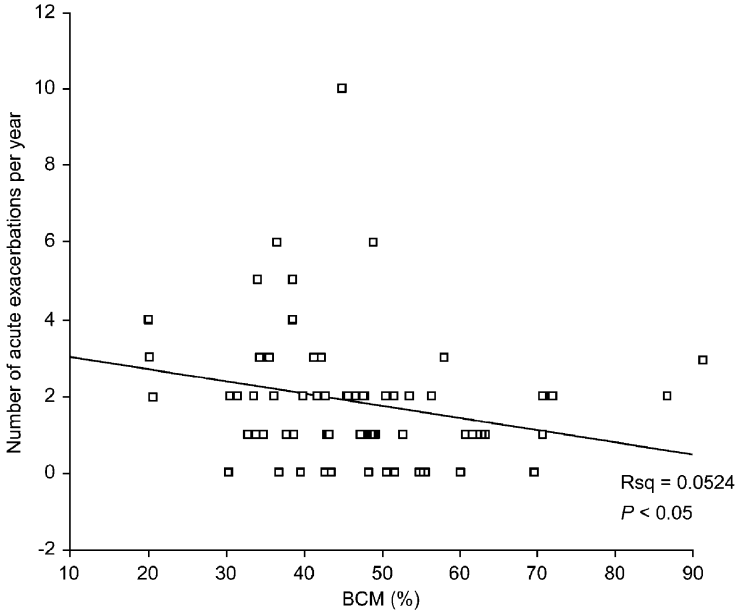

Figure 3 The relationship between body cell mass (BCM) and exacerbations (bacterial airway colonisation) in COPD patients with chronic respiratory failure (De Benedetto et al., unpublished data).

was found to correlate with a high rate of intensive-care-unit mortality.

In addition to the consequences of nutritional impairment on morbidity in COPD, the effect of low body weight on survival has been investigated. Several epidemiological studies have demonstrated malnutrition to be a strong predictor of mortality in patients with COPD. Indeed, there is a strong association between patients who experience significant weight loss, and the risk of death.[3,4,6,22,25,26] Taken together, these data provide unequivocal evidence that low body weight exerts a negative impact on outcomes in patients with COPD.

Muscle wasting and dysfunction: manifestations of another kind

The role of skeletal muscle dysfunction in COPD

The depletion of muscle mass and function are now recognised as important features of COPD, con-

tributing significantly to disease symptoms and prognosis. The presence of muscle dysfunction in COPD was first recognised in a study demonstrating that many patients with COPD have limited exercise capacity owing to skeletal muscle fatigue.[27] This finding challenged previous notions that such limitations were due to dyspnoea. Consequently, this observation fuelled extensive research in the field and many studies have since confirmed the role of skeletal muscle dysfunction in the pathogenesis of COPD.[28–30]

Mechanisms of skeletal muscle dysfunction

It is postulated that skeletal muscle dysfunction in COPD arises from two complex, inter-related events: muscle mass depletion caused by mitochondrial abnormalities and loss of contractile proteins; and muscle dysfunction or malfunction of the remaining muscle.[1] The pathophysiological mechanisms underlying skeletal muscle dysfunction have not been fully elucidated, however, and while nutritional imbalances have been shown to be involved, a host of other factors have also been implicated (Table 1).

At present, the relative contribution of each of these components and how they interact are unclear. Deconditioning is almost certainly an important contributor, given that patients with COPD have reduced physical activity, which results in further impairment in skeletal muscle function—leading to more symptoms at lower levels of work.[31] Medications such as oral corticosteroids also contribute to skeletal muscle dysfunction by causing skeletal muscle myopathy, an insidious disease leading to weakness mainly in the proximal muscles of the lower and upper limbs. Two different clinical patterns of steroid-induced myopathy are known—an acute form, which arises following short-term treatment with high doses of steroids, and a common, chronic form, which occurs after prolonged use with moderate doses.[32,33] The frequency of such events in patients treated with relatively low doses, whether in chronic treatment or in repetitive bursts during exacerbations, remains unclear. Nevertheless, a sedentary lifestyle, which is often adopted by COPD patients, may serve to exacerbate these effects.[1]

Table 1 Causes of muscle weakness in COPD.

Deconditioning	Systemic corticosteroids
Systemic inflammation	Hypoxaemia
Oxidative stress	Hypercapnia
Nutritional imbalance	Electrolyte disturbances
Reduced anabolic status	Cardiac failure

As adequate levels of anabolic hormones are required for normal muscle growth and development,[34] reports of substantially reduced levels of growth-promoting factors (e.g. insulin-like growth factor-1 (IGF-1)) and sex hormones (e.g. testosterone) have led to suggestions that such alterations may contribute to muscle dysfunction in COPD.[35] It is also speculated that elevated levels of systemic proinflammatory cytokines (e.g. TNF-α and interleukin-6 (IL-6)) observed in individuals with COPD play a role in the development of peripheral muscle weakness.[15,36] Indeed, it appears that there may be a correlation between peripheral muscle function and inflammation during the exacerbations experienced by patients with COPD.

The physiological changes that accompany exacerbations are known to contribute to respiratory muscle weakness.[37] To further investigate the contribution of these events to peripheral muscle weakness, and specifically the impact on muscle force, a recent study sought to define the clinical course of quadriceps force (QF) during an acute COPD exacerbation. Potential correlations with systemic inflammatory markers, such as IGF-1, IL-6, CXC chemokine ligand-8 (CXCL-8) and TNF-α in both hospitalised and stable COPD patients, were also defined.[36] The study revealed that muscle force was significantly reduced and subject to alterations in patients hospitalised with COPD, compared with patients with stable disease. Moreover, correlations between muscle force and systemic levels of IGF-1 and CXCL-8 were demonstrated, where QF was found to positively correlate with IGF-1 and negatively correlate with CXCL-8 in both hospitalised and stable COPD patients.[36] Changes in peripheral muscle force in COPD, and its relationship to systemic inflammatory markers require further investigation.[36]

Tissue hypoxia, through suppression of protein synthesis in muscle cells and alterations in structural (reduction in type I fibres) and functional (upregulation of mitochondrial cytochrome oxidase) components, as well as oxidative stress, electrolyte imbalance and comorbid conditions (e.g. cardiac failure), have also been implicated in skeletal muscle dysfunction, although their precise role remains to be fully established.

The pathophysiological mechanisms associated with muscle weakness are complex and additional studies will help to unravel the molecular and biochemical pathways underlying this systemic effect. Currently, physical inactivity is the only convincing factor that is known to contribute to muscle weakness in COPD.

Consequences of skeletal muscle dysfunction

Whatever the cause, muscle weakness has important consequences, including exercise limitation,[28,38,39] reduced QoL, enhanced utilisation of healthcare resources[40] and reduced survival.[41]

Traditionally, limitations in exercise performance in COPD were attributed to dyspnoea and reduced ventilatory capacity. However, several studies have since demonstrated that lung function alone cannot account for impaired exercise performance, and that peripheral and respiratory muscle weakness also contribute.[27,29] Low exercise tolerance has a large influence on health status in COPD[30] because physical deconditioning can lead to a marked reduction in a patient's ability to cope with activities of daily living, consequently leading to a reduction in QoL. Muscle weakness has also been found to be related to a high utilisation of healthcare resources.[40] In fact, weak correlations between muscle weakness and medical consumption (including steroid treatment) have been noted, although whether this relationship was causal merits further investigation.[40] Taken together, these data show that the burden of muscle dysfunction in COPD is significant.

Pulmonary rehabilitation: interventions aimed at improving disease outcome

Weight loss and muscle wasting have long been considered irreversible events. However, several reports in the literature describe the efforts that have been made in finding effective approaches to overcoming nutritional abnormalities and improving muscle function. Pulmonary rehabilitation programmes have been developed and implemented in COPD patients, with the primary aim of increasing exercise tolerance and improving quality of life. Key components of these programmes include exercise and muscle training and nutritional supplementation.

Management of malnutrition: assessing the role of nutritional supplementation

The rationale for treatment interventions aimed at increasing body weight is based on the observed relationship between weight loss, muscle wasting and muscle weakness.[6] Indeed, several studies have demonstrated that restoration of energy balance through nutritional supplementation results in a significant increase in body weight, fat-free mass and respiratory muscle function.[10,42–44] However, other studies failed to demonstrate such benefits following nutritional repletion.[45,46] To clarify the effect of nutritional support, a meta-analysis of numerous randomised controlled trials was conducted,[5] which revealed small, insignificant effects on anthropometric measures, lung function or functional exercise capacity among patients with COPD. These data are thus inconclusive, highlighting the need for additional studies using homogeneous populations of COPD patients who are selected for the same physical characteristics and severity of bronchial obstruction, in order to fully understand the merits of nutritional support.

Management of muscle dysfunction: assessing the role of exercise training

Given the contribution of peripheral and respiratory muscle weakness to exercise limitation, muscle training is an integral component of rehabilitation programmes.[28] Indeed, exercise training has been shown to improve exercise capacity in COPD patients.[47,48] Moreover, training has been shown to induce a partial improvement in oxidative capacity and exercise performance in peripheral muscles.[30] However, other studies revealed how a large fraction of patients (more than a third) failed to respond to a training programme.[49] Whether or not patients respond to a training programme may be related to levels of circulating cytokines,[50] but further characterisation of non-responders is required to determine the mechanisms underlying the absence of response.

Conclusions

This review underlines the role of systemic effects in the pathogenesis of COPD. Whilst tremendous progress has been made in defining the clinical implications of nutritional abnormalities and muscle dysfunction, further studies are required to gain a better understanding of the pathophysiological mechanisms giving rise to these effects. Resolving the complex systemic nature may allow current therapeutic approaches to be optimised and novel intervention strategies to be identified, leading to improvements in functionality, health status and prognosis of patients living with COPD.

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