

Chronic Obstructive Pulmonary Disease: Beyond Respiratory System

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Abstract

Chronic obstructive pulmonary disease (COPD) is defined as set of breathing related problems i.e. chronic bronchitis, expectoration and exertional dyspnea characterized by presence of airflow obstruction that is not fully reversible. However, COPD is a preventable and treatable disease with some extra pulmonary effects including skeletal muscle dysfunction, nutritional abnormalities and systemic inflammation that may contribute to the severity of the individual patients. The current clinical focus on respiratory symptom should be expanded to include assessment and prevention of diverse negative effects of the disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema is a progressive disease characterized by airflow limitation/obstruction that is either not reversible at all or only partially reversible. It is generally difficult to separate out the two conditions (chronic bronchitis and emphysema), hence these are grouped together as COPD^(1,2,3,4). The airflow obstruction in COPD is associated with abnormal inflammatory response of the lungs to chronic inhalational exposure from smokes, dusts and gases. This definition, as well as those published by many other societies and organizations focuses exclusively on the lungs. Recently, besides the typical pulmonary pathology of COPD (i.e. chronic bronchitis and emphysema), several effects occurring outside the lungs often associated with extra pulmonary abnormalities and have been described as the so called systemic effects of COPD. There is increasing realization that these systemic effects are clinically relevant and may contribute to better understanding and management of the disease. In the present review, extra pulmonary effects of COPD along with their potential mechanism and clinical implications have been discussed.

SYSTEMIC INFLAMMATION

It is currently accepted that an excessive/inadequate inflammatory response of the lungs to a variety of noxious inhaled gases or particles (mostly cigarette smoke) is a key pathogenic mechanism in COPD⁽⁵⁾. Various studies have

shown that the lung inflammatory response is characterized by: 1) increased numbers of neutrophils, macrophages and T-lymphocytes with a CD8+ predominance; 2) augmented concentrations of proinflammatory cytokines, such as leukotriene B4, interleukin (IL)-8 and tumor necrosis factor (TNF)-alpha, among others; and 3) evidence of oxidative stress caused by the inhalation of oxidants (tobacco smoke) and/or the activated inflammatory cells mentioned above⁽⁵⁾. It is less often realized that similar inflammatory changes can also be detected in the systemic circulation of these patients, including evidence of oxidative stress, the presence of activated inflammatory cells and increased plasma levels of proinflammatory cytokines.

NUTRITIONAL ABNORMALITIES

Malnutrition contributes to respiratory muscle weakness resulting in increased frequency of hospitalization, cor pulmonale and increased mortality. Several etiologies have been proposed for the nutritional deficiency observed in patients with COPD. Imbalance between energy intake and energy expenditure, due to decreased intake or increased expenditure, seems to be the factor involved in most cases⁽⁶⁾.

MECHANISMS OR CAUSES OF PROGRESSIVE WEIGHT LOSS: HYPOTHESES

1. Decreased food intake: Several studies have demonstrated that COPD patients consume more calories than estimated for normal people or by measured energy requirements.

Lewis and co-workers found that caloric intake was 150% of the calculated basal energy expenditure (BEE) in COPD patients with weight loss.

2. Elevated resting energy requirements: Malnourished COPD patients show incomplete metabolic adaptation to weight loss and have greater than predicted resting energy requirements.

Diet-induced thermogenesis: An obligatory energy expenditure occurs during assimilation of food into the body. This is abnormally elevated in malnourished COPD patients and contributes to their increased basal metabolic rate (BMR). Carbohydrate based diets (53% of calories from carbohydrates) cause a 20% rise in resting energy expenditure (REE) while fat based diets (55% of calories from fat) cause a 14% rise in REE.

Increased daily energy expenditure – energy cost of daily activities: The increased metabolic requirements in malnourished COPD patients are the result of the increased oxygen costs of augmented ventilation relative to 2.61 in normally nourished COPD patients. Hyperinflation with the associated mechanical disadvantage of the respiratory muscles, reduced ventilatory muscle strength and increased mechanical load, but also reduced ventilatory muscle efficiency.

The terms “malnourishment” and “cachexia” are often used indiscriminately in discussion of the nutritional abnormalities in COPD; however, important differences exist between these terms. As shown in (table I) both terms share several biochemical characteristics, but their origin and, importantly, response to dietary supplementation are very different. Several observations suggest that patients with COPD may suffer from cachexia rather than malnourishment. For instance, the caloric intake of patients with COPD is normal or even greater than normal, not lower, as in malnourishment; their metabolic rate is usually increased (7,8) whereas it is decreased in malnourished patients; and their response to nutritional support is often poor (9,10)

Figure 1

Table I: Comparison of malnourishment and cachexia

	Malnourishment	Cachexia
Fat triglyceride content	↓	↓
Skeletal muscle protein content	↓	↓
Origin	Decreased intake	?
Response to dietary supplementation	Good	Poor

↓ very reduced

SOURCE: A.G.N. Agustí et al Eur Respir J 2003; 21: 347–360

SKELETAL MUSCLE DYSFUNCTION

Skeletal muscle dysfunction is common in patients with COPD (11) It is characterized by specific anatomic changes (e.g., fiber-type composition and atrophy) and functional changes (e.g., strength, endurance, and enzyme activities) and contributes significantly to limited exercise capacity and reduced quality of life(11) The respiratory muscles, in particular the diaphragm, appear to behave quite differently from skeletal muscles in patients with COPD, from both the structural and functional points of view (11,12) The skeletal muscles are generally underused, whereas the diaphragm is constantly working against an increased load (13,14) Sedentarism, tissue hypoxia, and systemic inflammation are likely to be relevant pathogenic factors in skeletal muscle dysfunction

MUSCULOSKELETAL EFFECTS

The musculoskeletal system is among the extra pulmonary organ systems most frequently affected by chronic obstructive pulmonary disease (COPD) (15,12) Initially described as weight loss and cachexia, the involvement of the musculoskeletal apparatus in COPD is now better understood as a loss of fat-free mass (FFM) and bone mineral density (BMD) (16,17) Previous studies have described these processes separately and established the body mass index (BMI) as a predictor of loss of FFM and BMD (17,18) Increasing severity of COPD is found to be associated with decreasing FFM and BMD that includes progressive deconditioning and inactivity, greater number of exacerbations, increased use of corticosteroids, and increasing systemic inflammation

CARDIOVASCULAR EFFECTS

COPD increases the risk of cardiovascular disease by two- to threefold (19) For every 10% decrease in FEV₁, there is cardiovascular mortality increases by approximately 28% and risk of non-fatal coronary events increase by

approximately 20% in mild to moderate COPD. Besides reduced lung function is an independent and significant predictor of cardiovascular morbidity and mortality along with first-time stroke and fatal stroke⁽²⁰⁾ Several studies have shown that the endothelial function in COPD is abnormal in both pulmonary⁽²¹⁾ and systemic (renal) circulations^(22,23) Tobacco smoking is a shared risk factor for both COPD and cardiovascular disease. The inflammatory process seen in patients with COPD might be the mechanism responsible for this association⁽²⁴⁾

RENAL AND HORMONAL ABNORMALITIES

Renal and hormonal abnormalities, usually manifested as oedema or hyponatraemia, are encountered frequently in patients with chronic obstructive pulmonary disease. Edema in patients with COPD has been attributed to “cor pulmonale with backward heart failure”—that is, pulmonary hypertension induced by hypoxia and by structural changes in pulmonary arteries, increased systemic venous pressure, and reduced cardiac output. Experimental evidence has accumulated in support of the hypothesis that, in the advanced stages of COPD, imbalances in hormones that regulate body Na⁺ and water homeostasis—namely, the renin-angiotensin aldosterone axis and the arginine vasopressin system—are potential contributors to edema and hyponatraemia.⁽²⁵⁾ The most consistent alteration in renal function in hypoxemic hypercapnic patients with COPD is the reduction in Effective Renal Plasma Flow ERPF^(26,27) Table II summarizes the abnormalities of arterial blood gases, renal and hormonal indices during the progression of the disease.

Figure 2

Table II: Renal and Hormonal abnormalities in COPD during progression of disease

	Mild to severe	Very severe
Blood gases		
PaCO ₂	Hypercapnia	Hypercapnia
PaO ₂	Mild hypoxaemia	Severe hypoxaemia
Renal function		
ERPF	Reduced	Severely reduced
GFR	Normal	Reduced
Water excretion	Impaired	Markedly impaired
Sodium excretion	Impaired	Impaired
Hormones		
Catecholamines	Increased	Markedly impaired
PRA	Normal or increased	Increased
PA	Normal or increased	Increased
AVP	Normal	Increased
ANP	Normal	Increased
Sodium & Water homeostasis		
Oedema	Rare	Frequent
Hyponatraemia	Absent	Possible

PaCO₂ & PaO₂ = arterial oxygen and carbon dioxide tension, ERPF= effective renal plasma flow, FF = filtration fraction, GFR = Glomerular filtration rate, PRA = Plasma renin activity, A = plasma aldosterone, AVP = arginine vasopressin, ANP = atrial natriuretic peptide

SOURCE: Paolo Palange Thorax 1998;53;989-991

OSTEOSKELETAL EFFECTS

The prevalence of osteoporosis is increased in patients with COPD⁽²⁸⁾ Osteoporosis can have multiple causes, singly or in combination, including malnutrition, sedentarism, smoking, steroid treatment and systemic inflammation⁽²⁹⁾ Since most of them are already considered potential pathogenic factors of Skeletal muscle dysfunction in COPD, they could theoretically also contribute to osteoporosis, and, in this context, excessive osteoporosis in relation to age could also be considered a systemic effect of COPD⁽³⁰⁾

ENDOCRINAL DISTURBANCES

Disturbances in the anabolic hormone system may also impair the anabolic responses needed for skeletal muscle performance.

GROWTH HORMONE/INSULIN-LIKE GROWTH FACTOR-I

Growth hormone provides stimulation for muscle growth and development. In addition to increasing age, systemic corticosteroids (commonly used to treat COPD exacerbations) are known to down-regulate the growth hormone system⁽³¹⁾ IGF-I levels in stable COPD patients tend to be low⁽³²⁾ consistent with the impression that the growth hormone axis is suppressed by chronic disease. In COPD, physiological stress like chronic hypoxia and broncho constriction could possibly induce an increase in growth hormone.

THYROID HORMONE

An important function of thyroid hormone is regulation of metabolism and thermo genesis. Abnormalities in thyroid function potentially influence energy balance and body composition. Hyper metabolism is commonly observed in patients with COPD; this has been attributed to increased energy expenditure both at rest⁽³³⁾ and during physical activities⁽⁷⁾ A hyper metabolic state in combination with insufficient dietary intake will result in a negative energy balance and may conceivably contribute to weight loss in COPD⁽³⁴⁾ Low FEV₁ was associated with low basal and stimulated TSH levels⁽³⁵⁾

TESTOSTERONE

Accumulating data indicate that testosterone levels are low in COPD. The mechanism of these alterations is unclear, but it has been speculated that chronic hypoxia, disease severity, smoking, corticosteroid therapy and chronic (inflammatory) illness contribute to low testosterone levels. One of the suggested underlying factors for hypogonadism is

hypoxaemia, which is present in a portion of the COPD population. SEMPLE et al. found low testosterone levels in acutely ill, hospitalised COPD patients with hypoxaemia (Pa_{O2} ranging from 5–10 kPa). The degree of testosterone depression was correlated to the severity of arterial hypoxaemia and hypercapnia (36)

NERVOUS SYSTEM DEFECTS

The energy metabolism of the brain is altered in these patients (37). Patients with hypoxic COPD have evidence of a sub clinical parasympathetic autonomic neuropathy (38) with apparent preservation of sympathetic function. The abnormality may occur in stimulus reception, afferent nerve conduction, central processing, efferent nerve conduction, motor end-plate or end-organ (e.g. heart) response. Kinsman et al. showed a high frequency of sensory disturbances in COPD patients with few clinical signs (39). Cigarette smoking is a major etiological factor in the development of COPD and COPD-related peripheral neuropathy (40). It has several potential neurotoxic actions; carbon monoxide exacerbates tissue hypoxaemia, nicotine has stimulant actions and cyanogens may interfere with nerve function

PSYCHOLOGICAL DYSFUNCTION

Many patients with COPD develop psychological symptoms in addition to physical complaints. For example, depression (≤42%) (41) and anxiety (≤50%) (42) are two to three times more prevalent in COPD patients than in the general population (43). In addition, panic disorder may occur in as many as 32% of depressed patients with COPD (43,44). Indeed, studies have shown that anxiety and depression play a larger role in determining a patient's quality of life than COPD severity (45,46). Overall, psychological distress compounds the negative symptoms of COPD and other respiratory illnesses, resulting in longer hospital stays, adverse medical outcomes, and higher mortality rates (47). Patients with breathing disorders are predisposed to anxiety and depression, since symptoms of these three overlap. COPD patients who develop anxiety or depression face greater levels of cognitive decline (48), more functional limitations, lower self-efficacy, and more serious life events (43) than those with only breathing difficulties.

CLINICAL RELEVANCE

The systemic effects reviewed above are likely to have a profound clinical impact on the management of COPD. First, weight loss and skeletal muscle dysfunction clearly limit the exercise capacity of these patients and, therefore, have a direct negative effect on their quality of life. Second,

weight loss is a prognostic factor in patients with COPD that, importantly, is independent of other prognostic indicators, such as FEV₁ or Pa_{O2}, that assess the degree of pulmonary dysfunction (49,18). Thus, weight loss identifies a new systemic domain of COPD not considered by the traditional measures of lung function (50). These observations indicate, therefore, that in addition to the severity of lung disease, the clinical assessment of patients with COPD should take into consideration the extra pulmonary consequences of COPD, with weight loss being a critical indicator.

CONCLUSION

COPD must be considered a systemic disease, and the extra pulmonary manifestations must be considered in the evaluation of its severity. In addition, the treatment of these manifestations could modify the prognosis of these patients. Further studies elucidating the systemic manifestations, especially those affecting nutritional status and peripheral skeletal muscle function, are needed for the development of new treatment strategies, which might improve the exercise tolerance and the overall health status of these patients.

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