Systemic manifestations of chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a complex multisystem disease with comorbidities and systemic manifestations that affect respiratory symptoms, exacerbation frequency and mortality. This article gives an overview of these systemic manifestations and their importance, and offers strategies for managing them.

Chronic obstructive pulmonary disease is one of the most common respiratory diseases worldwide, with a European prevalence of between 2 and 10%. It is characterized by progressive and non-reversible airflow obstruction. The Global Initiative for Chronic Lung Disease (2011) defines chronic obstructive pulmonary disease as:

> **'a common, preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients'.**

Chronic obstructive pulmonary disease is not only thought to be associated with airway inflammation but also systemic inflammation (Aryal et al, 2013) and it is this systemic inflammation which is thought to be responsible for some of the systemic manifestations and comorbidities of the disease.

Comorbidities *vs* systemic effects

For the purpose of this review, comorbidities and systemic effects of chronic obstructive pulmonary disease will be used interchangeably. Current literature has identified difficulties in differentiating between these entities, which can result as a direct consequence of chronic obstructive pulmonary disease, its treatment or shared risk factors (Agusti and Soriano, 2008). It is more important for physicians to be aware of the 'chronic obstructive pulmonary disease syndrome' and be able to address the needs of the patient in front of them (Aryal et al, 2013).

Systemic manifestations are important as they contribute significantly toward the morbidity and mortality associated with chronic obstructive pulmonary disease. In the TORCH (Towards a Revolution in COPD Health) study, which studied 6100 patients with moderate to severe chronic obstructive pulmonary disease for 3 years, there were 911 deaths, which were attributed to respiratory failure or infection (35%), cardiovascular disease (26%) and cancer (21%, two-thirds were lung cancer). These findings have also been verified in autopsy series: one such study of 43 patients hospitalized with an exacerbation of chronic obstructive pulmonary disease who died within 24 hours, revealed cardiac failure was the most common cause of death (37%), followed by pneumonia (28%), venous thromboembolism (21%) and respiratory failure (14%).

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Possible theories underlying the chronic obstructive pulmonary disease 'syndrome'

The relationship between airway disease and systemic comorbidities in chronic obstructive pulmonary disease is thought to be the result of an upregulated inflammatory response but the exact mechanism still needs to be fully elucidated. There are two current theories in the literature: a spill over inflammatory effect from the lungs or a systemic inflammatory effect (Barnes and Celli, 2009).

The spill over hypothesis theorizes that there is a spill over of pro-inflammatory cytokines, e.g. interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF α), from the lungs which then creates a systemic inflammatory response. The lungs are viewed as the central stimulus to this process. The systemic inflammatory effect hypothesis theorizes that the lungs are a manifestation of systemic inflammation that also affects the other body systems. Neither theory has been proven but it is clear that although smoking is an independent risk factor for causing inflammation, chronic obstructive pulmonary disease itself is linked with increased levels of inflammation and this is related to worse outcomes (Nussbamer-Ochsner and Rabe, 2011). The upregulation of inflammation contributes to a diverse set of comorbidities (*Figure 1* and *Table 1*). These will now be discussed in more detail.

Cardiovascular disease

As most chronic obstructive pulmonary disease is attributed to cigarette smoking it is not surprising that these patients have a higher risk of cardiovascular events.

Interestingly, however, there is an increased risk of myocardial infarction in patients with chronic obstructive pulmonary disease independent of smoking status and there is greater risk in smokers who develop chronic obstructive pulmonary disease than smokers who do not (Sin et al, 2006). This is in keeping with the hypothesis that inflammation occurring in chronic obstructive pulmonary disease may be driving excess cardiovascular morbidity and mortality. A prospective study of 250 consecutive patients diagnosed with chronic obstructive pulmonary disease exacerbations and no evidence of coronary ischaemia underwent testing for brain natriuretic peptide (BNP) and troponin T on admission. Those with elevated levels of both had 15-fold higher all-cause mortality at 30 days (Chang et al, 2011), again highlighting the importance of the burden of cardiovascular disease in patients with chronic obstructive pulmonary disease.

In order to reduce the cardiovascular risk in people with chronic obstructive pulmonary disease, several therapeutic approaches have been trialled. Statins are increasingly recognized to have beneficial anti-inflammatory effects independent of their effect on cholesterol. In retrospective studies, use of statins was associated with a reduction in mortality after a chronic obstructive pulmonary disease exacerbation even in the absence of ischaemic heart disease (Søyseth et al, 2007). A systematic review has shown a benefit of statins in reducing the frequency of exacerbations, improving pulmonary functions and exercise capacity, and reducing all-cause and chronic obstructive pulmonary disease-related mortality (Janda et al, 2009).

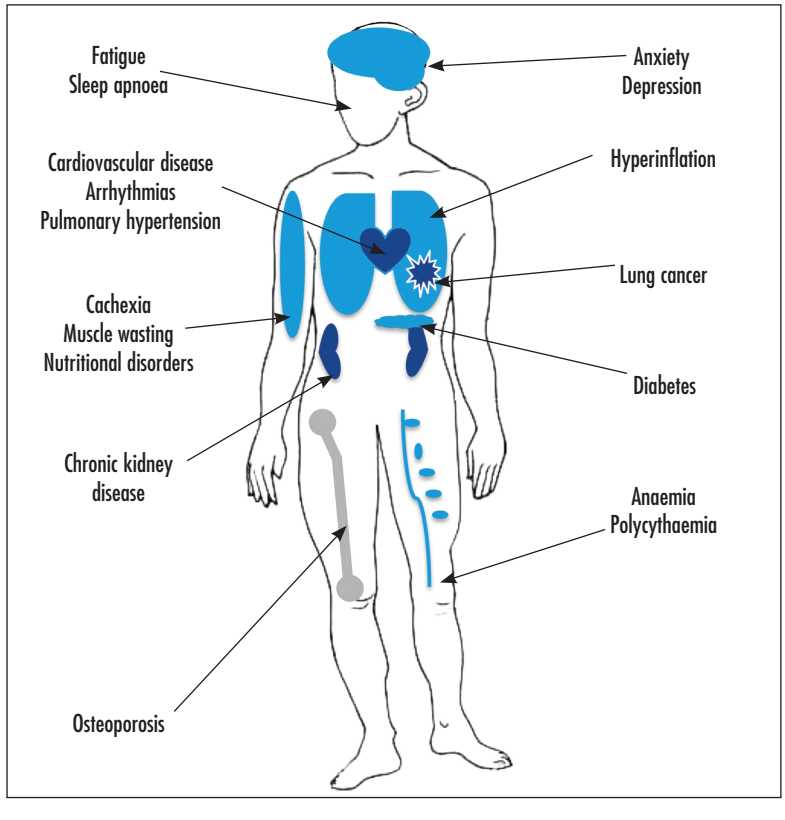
There has previously been a reluctance to use beta-blockers because of concern about worsening bronchospasm. Cardio-selective beta-blockers have preferential B1 effects and have been used in patients with chronic obstructive pulmonary disease without detrimental effect on lung function (Salpeter et al, 2005). In a primary care setting, patients with chronic obstructive pulmonary disease on beta-blockers had reduced mortality and risk of exacerbations (Rutten et al, 2010). Similarly, mortality of patients with chronic obstructive pulmonary disease admitted to hospital with an acute exacerbation was also reduced in those receiving a beta-blocker (Dransfield et al, 2008).

Exercise training has been shown to improve outcomes in cardiovascular disease and while there is good evidence for pulmonary rehabilitation in patients with chronic obstructive pulmonary disease, there are no clear data that pulmonary rehabilitation in these patients reduces cardiovascular morbidity. However, surrogate markers are increasingly used because of the rarity of cardiovascular endpoints. Arterial stiffness is one such endpoint which worsens with immobility and severe chronic obstructive pulmonary disease, and can be improved with exercise training (Vivodtzev et al, 2010). Whether this translates into a long-term benefit is yet to be determined.

Table 1. Systemic comorbidities in chronic obstructive pulmonary disease

Body system	Systemic manifestation
Cardiovascular	Heart failure
	Ischaemic heart disease
	Pulmonary hypertension
	Arrhythmias
Brain	Anxiety
	Depression
Musculoskeletal	Cachexia
	Muscle wasting and dysfunction
	Nutritional disorders
Bones	Osteoporosis
Haematological	Anaemia of chronic disease
	Polycythaemia
Sleep	Obstructive sleep apnoea
	Non-specific fatigue
Lungs	Hyperinflation
	Lung cancer
Renal	Chronic kidney disease
Systemic effects of exacerbations	Platelet activation
Systemic effects of therapy	Side effects associated with steroids

Figure 1. Schematic diagram of systemic comorbidities in chronic obstructive pulmonary disease.



Anxiety and depression

There is a complex interplay between physical and psychological symptoms in chronic obstructive pulmonary disease. Depression is common in chronic illness where quality of life is affected and understandably the feeling of being breathless can lead to anxiety. These two entities often overlap in patients with chronic obstructive pulmonary disease. Studies estimate the prevalence of depression to be in the order of 8–80% and anxiety 6–74% (Yohannes et al, 2010). These vary depending on the methods used to assess patients, as it is often not practical for formal psychiatric assessment for all patients. Common screening tools used are the Hospital Anxiety and Depression Scale and Geriatric Depression Score.

Rates of depression in patients with chronic obstructive pulmonary disease are higher than in those with other chronic illness such as coronary heart disease, stroke, diabetes, arthritis, hypertension and cancer (Schane et al, 2008). The presence of depressive symptoms is associated with a significantly worse 3-year mortality rate, probably as a result of a combination of poor compliance with therapy, increased smoking rates and reduced exercise capacity in those with chronic obstructive pulmonary disease and depression (Fan et al, 2007).

Airflow obstruction leads to air trapping and hyperinflation resulting in dyspnoea. This can limit activity and leads to increased anxiety and social isolation which leads to further deconditioning, worsening of symptoms and reducing quality of life (Cooper, 2006). An elevated score in the anxiety component of the Hospital Anxiety and Depression questionnaire in stable outpatients has been associated with increased frequency of exacerbations (Eisner et al, 2010).

More research is required on the optimum methods to treat depression and anxiety in patients with chronic obstructive pulmonary disease. Pharmacotherapy is effective at managing depression in other chronic illnesses such as ischaemic heart disease. Cognitive behavioural therapy can be useful, particularly for controlling symptoms of panic related to breathlessness (Livermore et al, 2010). A meta-analysis of six randomized controlled trials showed pulmonary rehabilitation significantly improved depression and anxiety (Coventry and Hind, 2007).

Wasting, skeletal muscle dysfunction and nutritional disorders in chronic obstructive pulmonary disease

It is a well-recognized phenomenon that patients with chronic obstructive pulmonary disease lose body mass; unexplained weight loss occurs in 10–15% with mild chronic obstructive pulmonary disease and 50% people with severe disease (Schols et al, 1993). Wasting occurs as a result of systemic inflammation mainly mediated by TNF-alpha (Wouters, 2002), but disuse atrophy also plays a role. Wasting is a poor prognostic marker independent of airflow limitation or hypoxia (Schols et al, 1998).

Patients with chronic obstructive pulmonary disease often have increased basal metabolic rate (Scholes et al, 1991) but also have a higher prevalence of malnutrition compared to individuals who do not have chronic obstructive pulmonary disease, leading to reduced performance and worse prognosis (Rutten et al, 2013). Malnutrition has a prevalence of up to 50% in severe chronic obstructive pulmonary disease. A decline in body weight is directly associated with a decline in forced expiratory volume in 1 second (FEV1).

In addition, in chronic obstructive pulmonary disease there is a loss of type 1 muscle fibres with an increase in type 2 muscle fibres and this contributes to fatigability and loss of endurance (Wouters, 2002). Skeletal muscle dysfunction is an independent predictor of mortality and morbidity in chronic obstructive pulmonary disease (Trooster et al, 2013) because the loss of muscle mass has an adverse effect on respiratory and peripheral muscle function and thus affects exercise capacity and health status. Loss of exercise endurance can precipitate a downward spiral leading to further disuse and wasting which can render patients immobile – this can be physically and mentally disabling (Man and Sin, 2006).

Treatment of cachexia in patients with chronic obstructive pulmonary disease is paramount to improve quality of life and survival. Patients with chronic obstructive pulmonary disease should be offered nutritional assessment and supplementation if necessary. The BODE (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) index can be used to predict mortality in these patients and comprises measures of body mass index, airflow obstruction, dyspnoea and 6-minute walk distance. Physical exercise has beneficial effects in increasing muscle mass, increasing strength and improving body composition (Rutten et al, 2013) and therefore referring patients for pulmonary rehabilitation should be considered, as this improves the BODE index as a whole (Cote and Celli, 2005).

Osteoporosis

Patients with chronic obstructive pulmonary disease often have multiple risk factors for reduced bone density such as advanced age, immobility, low body mass index, cigarette smoking and long-term steroid use (Ferguson et al, 2009). In one study, bone mineral density at baseline was reduced in 65% of participants (osteopenia or osteoporosis) and 18% of men and 30% of women had osteoporosis.

Long-term oral steroids reduce bone density in a dose-dependent manner. Inhaled corticosteroids at conventional doses do not affect bone density, but at higher doses (budesonide 800 μg/day, fluticasone 750 μg/day and beclomethasone 1000 μg/day) they increase markers of bone turnover (Langhammer et al, 2009). With reduced bone density there is an increased risk of fractures. Hip fractures can cause significant mortality and morbidity and lead to further reduced mobility. Vertebral osteoporotic crush fractures can lead to thoracic kyphosis

and worsening of pulmonary function. Approximately 40% of patients with chronic obstructive pulmonary disease have at least one vertebral crush fracture and the prevalence increases with severity of chronic obstructive pulmonary disease in men (Nuti et al, 2009).

In the absence of guidelines specific to the management of osteoporosis in those with chronic obstructive pulmonary disease treatment is as for the general population with calcium and vitamin D supplementation, and bisphosphonates if required.

Anaemia and chronic obstructive pulmonary disease

Anaemia is present in 15–20% of patients with chronic obstructive pulmonary disease, whereas only 6% have polycythaemia (Barnes and Celli, 2009). This anaemia is classified as anaemia of chronic disease, and is caused by the inflammatory component of chronic obstructive pulmonary disease (Similowski et al, 2006). Pro-inflammatory cytokines and chemokines interfere with haematopoesis in several ways, with reduced red blood cell life expectancy, impaired use of iron and blunted response to erythropoietin. The presence of anaemia worsens dyspnoea and exercise tolerance, reducing functional capacity (Cote et al, 2007), and is a negative prognostic indicator.

Treatment of anaemia in chronic obstructive pulmonary disease is difficult as the systemic inflammatory process makes the body resistant to erythropoetin and iron supplements are not metabolized effectively and may increase oxidative stress. Blood transfusion has shown reductions in minute ventilation and work of breathing in chronic obstructive pulmonary disease (Similowski et al, 2006), but whether this affects mortality is yet to be demonstrated. Owing to the lack of evidence blood transfusions for the treatment of anaemia should be decided on an individual patient basis.

Sleep and chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease affects sleep quality in two main ways:

1. It can have an effect on nocturnal hypoxia
2. It can present as an 'overlap' syndrome with obstructive sleep apnoea.

Sleep has effects on breathing which include changing central respiratory control, changing lung mechanics and causing changes in muscle contractility (McNicholas, 2000). In healthy individuals these changes have no effect, but in those with chronic obstructive pulmonary disease the physiological changes of sleep lead to an exacerbation of hypoxaemia and hypercapnia. This exaggerated hypoxia and hypercapnia can cause sleep disturbance and lead to daytime symptoms of chronic fatigue and lethargy which have a detrimental effect on overall impairment in the quality of life (Breslin et al, 1998). Management of respiratory insufficiency during sleep relies on the optimization of underlying chronic obstructive pulmonary disease.

Table 2. Targeted therapies for respiratory insufficiency during sleep

Intervention	Effect
Anticholinergics	Counteract cholinergic tone that increases at night. May improve airway obstruction and hypoxaemia
Theophyllines	Beneficial in chronic hypoventilation, stimulating diaphragm contractility and central respiratory control
Nocturnal non-invasive ventilation	Ventilatory support can improve gas exchange during wakefulness as well as during the night. Potential effects on respiratory muscle strength and endurance

Some specific pharmacological therapies have been suggested and these are listed in *Table 2*.

Chronic obstructive pulmonary disease and obstructive sleep apnoea are two of the most prevalent respiratory disorders worldwide, and 'overlap syndrome' is a term used to describe the co-existence of the two disorders (Marin et al, 2010). The two disorders do not co-exist because of a shared pathophysiology but because of the prevalence of each disorder (Weitzenblum et al, 2009). Patients with overlap syndrome have a worse prognosis than sufferers of the individual diseases and have an increased risk of hospitalization with an exacerbation of chronic obstructive pulmonary disease (Marin et al, 2010). Overlap syndrome patients also have a greater degree of hypoxaemia and hypercapnia than FEV1-matched individuals without obstructive sleep apnoea, and have a higher risk of severe pulmonary hypertension and right heart failure (Chaouat et al, 1995). Cardiovascular risk also increases in overlap syndrome and this may be related to increased oxidative stress caused by both disorders (McNicholas, 2009).

Factors that may potentiate obstructive sleep apnoea in chronic obstructive pulmonary disease are cigarette smoking and medication, e.g. steroids. However, many patients with chronic obstructive pulmonary disease are protected against obstructive sleep apnoea because they have a low body mass index, reduced REM sleep and maybe because they are on medications such as theophyllines.

Management of overlap syndrome relies on optimization of the management of the underlying chronic obstructive pulmonary disease and referring for specialist input. Continuous positive airway pressure treatment is associated with increased survival and decreased hospitalization in overlap syndrome (Marin et al, 2010).

Diabetes

In patients with chronic obstructive pulmonary disease there is a two-fold increase in type 2 diabetes even in mild disease (Rana et al, 2004) and it is thought that insulin resistance results from systemic inflammation. Oral steroids increase the risk of diabetes, but in a study of inhaled corticosteroids current use was associated with a 34% increase in the rate of diabetes. This risk was greatest with high doses of inhaled corticosteroids (equivalent to 1000 μg per day of fluticasone) (Suissa et al, 2010).

Lung cancer and chronic obstructive pulmonary disease

Lung cancer is one of the world's leading causes of preventable death and 20% of cancer deaths in Europe are attributable to it. Chronic obstructive pulmonary disease and lung cancer share the strong risk factor of smoking but smokers with chronic obstructive pulmonary disease are 3–4 times more likely to develop lung cancer than smokers with normal lung function (Barnes and Celli, 2009). Chronic obstructive pulmonary disease is therefore recognized as an independent risk factor for developing lung cancer (Young et al, 2009) and only modest reductions in FEV1 can provide a strong predictor of lung cancer development (Wasswa-Kintu et al, 2005). This association between FEV1 and lung cancer is even more prevalent in women, although the exact reason for this is unknown. The increased risk of lung cancer in chronic obstructive pulmonary disease is linked to the systemic inflammation and oxidative stress that the disease causes (Sin et al, 2006). Some authors have postulated that there is a genetic susceptibility in certain individuals to the effects of systemic inflammation and that these patients are more likely to develop lung cancer. In addition to systemic inflammation, radiological evidence of emphysema and hyper-expansion are also recognized as important risk factors for lung cancer (Hardavella and Spiro, 2013).

The leading causes of death in mild to moderate chronic obstructive pulmonary disease are lung cancer and cardiovascular disease (Sin et al, 2006), therefore addressing the link between chronic obstructive pulmonary disease and lung cancer is incredibly important in reducing morbidity and mortality. Chronic obstructive pulmonary disease tends to be associated with an increased risk of small cell carcinoma and squamous cell carcinoma as opposed to adenocarcinoma. Doctors need to be alert to the diagnosis of a potential underlying malignancy and recognize that even patients with mild chronic obstructive pulmonary disease are at a much higher risk.

Treatment of lung cancer and chronic obstructive pulmonary disease also poses some difficulties. A decline in lung function can have implications for the scope of treatment that can be offered as patients may not be fit for surgery or radical treatment as a result of their performance status. A multidisciplinary team approach to care is imperative so the best available and appropriate treatment can be offered to patients with lung cancer and chronic obstructive pulmonary disease.

Systemic effects of infections and exacerbations

Airway infections and exacerbations play a key role in the natural history of chronic obstructive pulmonary disease and have an effect on systemic comorbidities associated with chronic obstructive pulmonary disease (Singh et al, 2013). Exacerbations can directly worsen airway inflammation and function as well as contributing to comorbidities, such as upregulation of platelet activation that may precipitate an acute ischaemic event (Singh et al, 2013).

Patients with chronic obstructive pulmonary disease are at increased risk of pneumonia because of the nature of their airways disease and this risk may be further increased with the use of inhaled corticosteroids (Crim et al, 2009). The symptoms of a chronic obstructive pulmonary disease exacerbation may mimic those of pneumonia and therefore careful clinical assessment and radiography is needed. Recurrent pneumonia can lead to further structural lung damage and there is then a risk that patients will be colonized with typical and atypical micro-organisms, further contributing to local and systemic inflammation.

Conclusions

Chronic obstructive pulmonary disease is a multisystem disease and physicians managing these individuals should not only focus on pharmacological therapy but should also pay careful attention to comorbidities and manage the patient in a combined multidisciplinary team in order to address the syndrome of chronic obstructive pulmonary disease. Diagnosis and treatment of these comorbidities can improve quality of life and reduce the mortality for patients with chronic obstructive pulmonary disease. **BJHM**

KEY POINTS

- When assessing a patient with a 'chronic obstructive pulmonary disease exacerbation', pay careful attention to signs of heart failure, lung cancer, pneumonia and venous thromboembolism which are common causes of mortality.
- Cardiovascular disease is a huge cause of morbidity and mortality in patients with chronic obstructive pulmonary disease. Risk can be reduced with statins and cardioselective beta-blockers have a favourable effect on mortality.
- Anxiety and depression may often manifest as breathlessness and frequent admissions, all chronic obstructive pulmonary disease admissions should be screened for these.
- Osteoporosis and reduced muscle mass from cachexia occur frequently in patients with chronic obstructive pulmonary disease. These can increase risk of falls and fractures resulting in further immobility, pain and reduced exercise capacity.
- Pulmonary rehabilitation has multiple benefits, not only improving exercise capacity and exacerbation rate but also improving muscle strength and mood disturbances.

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